```
=> fil lreg

FILE 'LREGISTRY' ENTERED AT 11:47:39 ON 30 NOV 2004
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LREGISTRY IS A STATIC LEARNING FILE

=> fil reg

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STRUCTURE FILE UPDATES:   28 NOV 2004  HIGHEST RN 790189-55-8
DICTIONARY FILE UPDATES:  28 NOV 2004  HIGHEST RN 790189-55-8

TSCA INFORMATION NOW CURRENT THROUGH MAY 21, 2004

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

=> fil marpat

FILE 'MARPAT' ENTERED AT 11:47:44 ON 30 NOV 2004
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FILE CONTENT: 1988-PRESENT (VOL 141 ISS 22)(20041126/ED)

MOST RECENT CITATIONS FOR PATENTS FROM FIVE MAJOR ISSUING AGENCIES
(COVERAGE TO THESE DATES IS NOT COMPLETE):

US    6800776 05 OCT 2004
DE   10314780 30 SEP 2004
EP    1464371 06 OCT 2004
JP 2004260057 16 SEP 2004
WO 2004087649 14 OCT 2004

Structure search limits have been raised.  See HELP SLIMIT for the new,
higher limits.

=> fil hcap

FILE 'HCAPLUS' ENTERED AT 11:47:47 ON 30 NOV 2004
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FILE COVERS 1907 - 30 Nov 2004 VOL 141 ISS 23
FILE LAST UPDATED: 28 Nov 2004 (20041128/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> file stnguide

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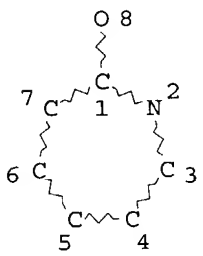
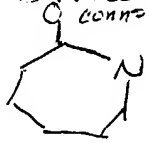
FILE CONTAINS CURRENT INFOR
LAST RELOADED: Nov 26, 2004

=> d que l21
L1 STR



Marpat-based search

L1: STR to search in Marpat
L2: search in Marpat
L13: Retrieve corresponding HCAPLUS records
- all of these # hits have at least one Markush structure containing



L15-L21: limit w/ text

NODE ATTRIBUTES:
CONNECT IS E1 RC AT 8
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 8

STEREO ATTRIBUTES: NONE

L2	3008	SEA FILE=MARPAT SSS FUL L1
L13	3008	SEA FILE=HCAPLUS ABB=ON PLU=ON L2
L14	15819	SEA FILE=HCAPLUS ABB=ON PLU=ON ?METALLOPROTEAS? OR MMP?
L15	28	SEA FILE=HCAPLUS ABB=ON PLU=ON L13 AND L14
L16	1441184	SEA FILE=HCAPLUS ABB=ON PLU=ON ?MERCAPT? OR ?THIO? OR ?SULFENYL? OR ?CYSTYL? OR ?CYSTEIN? OR ?SULFAN? OR ?SULFID?
L17	1073	SEA FILE=HCAPLUS ABB=ON PLU=ON L13 AND L16

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L18          14 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L15 AND L17
L21          28 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L18 OR L15


=> d iall hitstr l21
YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS' - CONTINUE? (Y)/N:y


L21  ANSWER 1 OF 28  HCAPLUS  COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER:         2004:625347  HCAPLUS
DOCUMENT NUMBER:          141:157040
ENTRY DATE:               Entered STN:  04 Aug 2004
TITLE:                    1-carboxylmethyl-2-oxo-3-acylaminoazepans useful as
                          selective inhibitors of MMP-12 matrix
                          metalloproteinase
INVENTOR(S):              Warshawsky, Alan M.; Janusz, Michael J.
PATENT ASSIGNEE(S):       Aventis Pharmaceuticals Inc., USA
SOURCE:                   U.S., 29 pp.
                          CODEN: USXXAM
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
INT. PATENT CLASSIF.:
            MAIN:         C07D223-12
       SECONDARY:         C07D401-00; C07D405-00; C07D409-00; A61K031-55
US PATENT CLASSIF.:       514212030; 514212080; 540524000; 540527000
CLASSIFICATION:           27-21 (Heterocyclic Compounds (One Hetero Atom))
                          Section cross-reference(s): 1, 63
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.          DATE
     --------------       ----   --------    --------------------     --------
     US 6770640            B1    20040803    US 1999-467292           19991217
PRIORITY APPLN. INFO.:                       US 1998-155205P      P   19981231
PATENT CLASSIFICATION CODES:
 PATENT NO.       CLASS  PATENT FAMILY CLASSIFICATION CODES
 --------------   -----  ----------------------------------------------
 US 6770640       ICM    C07D223-12
                  ICS    C07D401-00; C07D405-00; C07D409-00; A61K031-55
                  NCL    514212030; 514212080; 540524000; 540527000
 US 6770640       ECLA   C07D223/12; C07D403/12+223+209
OTHER SOURCE(S):          MARPAT 141:157040
GRAPHIC IMAGE:
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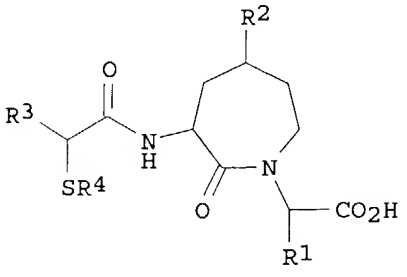

I

ABSTRACT:
Title compds. [I; R1 = H, alkyl, CH2SCH2NHAc, (CH2)pA, (CH2)mB, CHDR7; A = aryl, heteroaryl, cyclohexyl; B = N(R7)2, guanidino, nitroguanidino, CO2R6, CONR6; D = O, S; R2 = alkyl, (CH2)pheteroaryl, (CH2)pAr; Ar = (substituted) Ph, naphthyl; R3 = W(CH2)m, QZ(CH2)m; W = phthalimido; Q = H, Y(CH2)n; Z = O, NR6, CONR6, SO2NR6, etc.; Y = H, aryl, heteroaryl, CO2R6, N(R6)2, morpholino, piperidino, pyrrolidino, isoindolyl; R4 = H, COR7, CO(CH2)qK, SG; G = pyridinyl(alkyl), azolylalkyl, phenylalkyl, etc.; K = morpholino, piperidino, pyrrolidino, imidazolyl, pyridinyl, etc.; R6 = H, alkyl; R7 = H, alkyl, (CH2)pAr; m = 2-4; n = 0-4; p = 0-2], were claimed (no synthetic or biol. data).

SUPPL. TERM: carboxylmethyloxoacylaminoazepan **MMP12** matrix metalloproteinase inhibitor; emphysema smoking induced treatment azepan carboxymethyl oxo acylamino

INDEX TERM: Drug delivery systems
Human
(1-carboxylmethyl-2-oxo-3-acylaminoazepans useful as selective inhibitors of **MMP**-12 matrix metalloproteinase)

INDEX TERM: Emphysema
(treatment of smoking induced emphysema; 1-carboxylmethyl-2-oxo-3-acylaminoazepans useful as selective inhibitors of **MMP**-12 matrix metalloproteinase)

INDEX TERM: 9004-06-2, **MMP** 12
ROLE: BSU (Biological study, unclassified); BIOL (Biological study)
(**MMP**-12 inhibitors; 1-carboxylmethyl-2-oxo-3-acylaminoazepans useful as selective inhibitors of **MMP**-12 matrix metalloproteinase)

INDEX TERM: 60-32-2, 6-Aminohexanoic acid 15100-75-1, (S)-Phenylalanine tert-butyl ester hydrochloride 90719-32-7, (S)-4-Benzyl-2-oxazolidinone 143365-54-2
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(carboxylmethylacylaminoazepanones useful as selective inhibitors of **MMP**-12 matrix metalloproteinase)

INDEX TERM: 4443-26-9P, 6-Phthalimidohexanoic acid 5107-16-4P 205391-14-6P 205391-15-7P 205391-16-8P 205391-17-9P 205391-18-0P 205391-19-1P
ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(carboxylmethylacylaminoazepanones useful as selective inhibitors of **MMP**-12 matrix metalloproteinase)

INDEX TERM: 731851-42-6P 731851-43-7P 731851-44-8P
ROLE: SPN (Synthetic preparation); PREP (Preparation)
(carboxylmethylacylaminoazepanones useful as selective inhibitors of **MMP**-12 matrix metalloproteinase)

REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD.

REFERENCE(S):
(1) Anon; EP 0726072 1996 HCAPLUS
(2) Anon; EP 0599444 1998 HCAPLUS
(3) Anon; WO 9812211 1998 HCAPLUS
(4) Anon; WO 9935145 1999 HCAPLUS
(5) Karanewsky; US 5552397 A 1996 HCAPLUS
(6) Neustadt; US 5075302 A 1991 HCAPLUS
(7) Robl; US 5654294 A 1997 HCAPLUS
(8) Robl; US 5856476 A 1999 HCAPLUS
(9) Robl; J Am Chem Soc 1994, V116, P2348 HCAPLUS

(10) Robl; J Med Chem 1996, V39, P494 HCAPLUS
(11) Robl; Tetrahedron Lett 1994, V35(9), P1393 HCAPLUS
(12) Robl; Tetrahedron Lett 1996, V37(50), P8985 HCAPLUS
(13) Warshawsky; Bioorg Med Chem Lett 1996, V6(8), P957 HCAPLUS

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=> d ibib abs ed hitind hitstr retable l21 2
YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS' - CONTINUE? (Y)/N:y

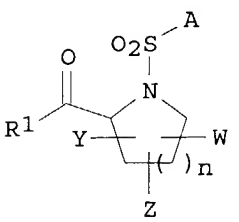
L21 ANSWER 2 OF 28 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:569862 HCAPLUS
DOCUMENT NUMBER: **141:123901**
TITLE: Preparation of N-sulfonyl-cyclic amine-2-carbohydroxamic acid derivatives as **metalloprotease** inhibitors
INVENTOR(S): Natchus, Michael George; De, Biswanath; Pikul, Stanislaw; Almstead, Neil Gregory; Bookland, Roger Gunnard; Taiwo, Yetunde Olabisi; Cheng, Menyan
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 42 pp., Cont.-in-part of U.S. Ser. No. 186,531.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004138260	A1	20040715	US 2003-730572	20031208
US 6417219	B1	20020709	US 1997-918317	19970826
US 2002061877	A1	20020523	US 2001-888675	20010625
US 6569855	B2	20030527		
US 2002072517	A1	20020613	US 2001-888759	20010625
US 2003105153	A1	20030605	US 2002-186531	20020701
US 2003191163	A1	20031009	US 2002-308780	20021203
JP 2004115531	A2	20040415	JP 2003-384116	20031113

PRIORITY APPLN. INFO.:

US 1996-24842P	P	19960828
US 1997-918317	A3	19970826
US 2001-888675	A2	20010625
US 2001-888759	B2	20010625
US 2002-186531	A2	20020701
JP 1998-511715	A3	19970822

OTHER SOURCE(S): MARPAT 141:123901
GI



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AB The invention provides compds. according to formula (I), in particular N-sulfonylpyrrolidine-2-carbohydroxamic acid derivs., [wherein A = each (un)substituted alkyl, heteroalkyl, aryl, or heteroaryl; R1 = NHOR2 (where R2 = H, alkyl); W = one or more of H, lower alkyl, or an alkylene bridge that forms a ring in addition to the main ring; Y = independently one or more of HO, SR3, SOR4, SO2R8, alkoxy, or (un)substituted amino (where R8 = alkyl, aryl, heteroaryl, heteroalkyl, amino, alkylamino, dialkylamino, arylamino, diarylamino, alkylarylamino); Z = H, HO, or alkyl, or an alkylene or heteroalkylene bridge that forms a ring in addition to the main ring; n = 1; some provisos applied], pharmaceutically-acceptable salts, biohydrolyzable amides, esters, or imides thereof are prepared These compds. are useful as inhibitors of **metalloproteases**, and effective in treating conditions characterized by excess activity of these enzymes, in particular restenosis. Thus, cis-hydroxy-D-propine was condensed with 4-methylphenylsulfonyl chloride in the presence of Et3N and 2,6-dimethylpyridine in aqueous dioxane at room temperature for 14 h gave N-(4-methylphenylsulfonyl)-cis-hydroxy-D-propine which was esterified with MeOH and SOCl2 to give N-(4-methylphenylsulfonyl)-cis-hydroxy-D-propine Me ester which was treated with hydroxylamine monopotassium salt in MeOH overnight to give (2R,4S)-1-(4-Methoxyphenylsulfonyl)-2-(N-hydroxycarboxamido)-4S-hydroxypyrrolidine.

ED Entered STN: 16 Jul 2004

IC ICM A61K031-445
ICS A61K031-454; A61K031-4025; A61K031-4015

NCL 514317000; 514326000; 514422000; 514423000

CC 34-2 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1, 7

ST restenosis treatment phenylsulfonylpyrrolidinecarbohydroxamic acid prepn; phenylsulfonylpyrrolidinecarbohydroxamic acid prepn **metalloprotease** inhibitor; sulfonyl cyclic amine carbohydroxamic acid prepn **metalloprotease** inhibitor

IT Amines, preparation
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(cyclic; preparation of N-sulfonyl pyrrolidine-2-carbohydroxamic acid as **metalloprotease** inhibitors for treatment of restenosis)

IT Human
(preparation of N-sulfonyl pyrrolidine-2-carbohydroxamic acid as **metalloprotease** inhibitors for treatment of restenosis)

IT Artery, disease
(restenosis; preparation of N-sulfonyl pyrrolidine-2-carbohydroxamic acid as **metalloprotease** inhibitors for treatment of restenosis)

IT 1138-54-1P, 4-(Isobutoxy)phenylsulfonyl chloride 57850-07-4P, 1-(4-Methylphenylsulfonyl)-(2R)-carbomethoxy-(4R)-hydroxypyrrolidine 64700-65-8P, (2R)-2-Methoxycarbonyl-5-pyrrolidinone 182937-63-9P, (2R)-2-Benzyloxy-3-phenylpropanoic acid 203934-42-3P, 1-(4-Methoxyphenylsulfonyl)-(2R)-carbomethoxy-4-oxopyrrolidine 203934-63-8P, 1-(4-Butoxyphenylsulfonyl)-(2R)-carbomethoxy-(4R)-hydroxypyrrolidine 203994-66-5P, 1-(4-Methoxyphenylsulfonyl)-(2R)-carboxy-(4R)-hydroxypyrrolidine 203994-80-3P, 1-(4-Methoxyphenylsulfonyl)-(2R)-carbomethoxy-(4R)-hydroxypyrrolidine 203994-82-5P, 1-(4-Methoxyphenylsulfonyl)-(2R)-carbomethoxy-(4S)-**acetylthiopyrrolidine** 204072-15-1P, 1-(4-Methoxyphenylsulfonyl)-(2R)-carbomethoxy-(4S)-benzoyloxypyrrolidine 204072-16-2P, 1-(4-Methoxyphenylsulfonyl)-(2S)-carbomethoxy-(4R)-hydroxypyrrolidine 204072-17-3P, 1-(4-Methoxyphenylsulfonyl)-(2S)-carbomethoxy-(4S)-hydroxypyrrolidine 204072-18-4P, 1-(4-Methoxyphenylsulfonyl)-(2R)-

carboxy-(4S)-hydroxypyrrolidine 204072-19-5P, 1-(4-Methoxyphenylsulfonyl)-(2R)-carbomethoxy-(4S)-methoxypyrrolidine 204072-20-8P, 1-(4-Methoxyphenylsulfonyl)-(2R)-carbomethoxy-(4R)-[(trifluoromethanesulfonyl)oxy]pyrrolidine 204072-21-9P, 1-(4-Methoxyphenylsulfonyl)-(2R)-carbomethoxy-(4S)-(2-**benzothiazolylthio**)pyrrolidine 204072-22-0P, 1-(4-Methoxyphenylsulfonyl)-(2R)-carbomethoxy-(4S)-hydroxypyrrolidine 204072-23-1P, 1-(4-Methoxyphenylsulfonyl)-(2R)-carbomethoxy-(4R)-(2-**benzothiazolylthio**)pyrrolidine 204072-24-2P, 1-(4-Methoxyphenylsulfonyl)-(2R)-carbomethoxy-(4S)-(1-methyl-2-**imidazolylthio**)pyrrolidine 204072-25-3P, 1-(4-Methoxyphenylsulfonyl)-(2R)-carbomethoxy-(4R)-(1-methyl-2-**imidazolylthio**)pyrrolidine 204072-26-4P, 1-(4-Methoxyphenylsulfonyl)-(2R)-carbomethoxy-(4S)-phenoxypyrrolidine 204072-27-5P, 1-(4-Methoxyphenylsulfonyl)-(2R)-carbomethoxy-(4S)-[4-(benzyloxy)phenoxy]pyrrolidine 204072-28-6P, 1-(4-Methoxyphenylsulfonyl)-(2R)-carbomethoxy-(4S)-(3-phenylaminophenoxy)pyrrolidine 204072-29-7P, 1-(4-Methoxyphenylsulfonyl)-(2R)-carbomethoxy-(4S)-(3-pyridinyloxy)pyrrolidine 204072-30-0P, 1-(4-Methoxyphenylsulfonyl)-(2R)-carbomethoxy-(4S)-**phenylthiopyrrolidine** 204072-32-2P, 1-(4-Methoxyphenylsulfonyl)-(2R)-carbomethoxy-(4S)-(4-**methoxyphenylthio**)pyrrolidine 204072-34-4P, 1-(4-Methoxyphenylsulfonyl)-(2R)-carbomethoxy-(4S)-(3-**methoxyphenylthio**)pyrrolidine 204072-36-6P, 1-(4-Methoxyphenylsulfonyl)-(2R)-carbomethoxy-(4R)-ethoxymethoxypyrrolidine 204072-37-7P, 1-(4-Methoxyphenylsulfonyl)-(2R)-carbomethoxy-(4R)-benzyloxymethoxypyrrolidine 204072-38-8P, 1-(4-Methoxyphenylsulfonyl)-(2R)-carbomethoxy-(4R)-[(2-methoxyethoxy)methoxy]pyrrolidine 204072-39-9P 204072-40-2P, 1-(4-Methoxyphenylsulfonyl)-(2R)-carboxy-4-oxopyrrolidine 204072-41-3P, 1-(4-Methoxyphenylsulfonyl)-(2R)-carbomethoxy-(4R)-4-hydroxy-4-ethylpyrrolidine 204072-42-4P, 1-(4-Methoxyphenylsulfonyl)-(2R)-carbomethoxy-(4R)-4-hydroxy-4-phenylpyrrolidine 204072-44-6P, 1-(4-Methoxyphenylsulfonyl)-(2R)-carbomethoxy-3,3-dimethyl-4-oxopyrrolidine 204072-45-7P, 1-(4-Methoxyphenylsulfonyl)-(2R)-carbomethoxy-3,3-dimethyl-(4R)-hydroxypyrrolidine 204072-46-8P, 1-(3,4-Dimethoxyphenylsulfonyl)-(2R)-carbomethoxy-(4R)-hydroxypyrrolidine 204072-47-9P, 1-(2-Nitro-4-methoxyphenylsulfonyl)-(2R)-carbomethoxy-(4R)-hydroxypyrrolidine 204072-50-4P, 1-(4-Bromobenzenesulfonyl)-(2R)-carbomethoxy-(4R)-hydroxypyrrolidine 204072-51-5P, 1-(2-Methyl-4-bromobenzenesulfonyl)-(2R)-carbomethoxy-(4R)-hydroxypyrrolidine 204072-52-6P, 1-(2,4-Dichlorophenylsulfonyl)-(2R)-carbomethoxy-(4R)-hydroxypyrrolidine 204072-53-7P, 4-(2-Methoxyethoxy)phenylsulfonyl chloride 204072-56-0P, 1-(4-Isobutyloxyphenylsulfonyl)-(2R)-carbomethoxy-(4R)-hydroxypyrrolidine 204072-57-1P, 1-(2-Methyl-4-bromophenylsulfonyl)-(2R)-carbomethoxy-(4S)-(3-**methoxyphenylthio**)pyrrolidine 204072-58-2P, 1-(4-Butoxyphenylsulfonyl)-(2R)-carbomethoxy-(4S)-(2-**benzothiazolylthio**)pyrrolidine 204072-59-3P, 1-(2-Nitro-4-methoxyphenylsulfonyl)-(2R)-carbomethoxy-(4S)-(2-**benzothiazolylthio**)pyrrolidine 204072-60-6P, 1-(4-Butoxyphenylsulfonyl)-(2R)-carbomethoxy-(4S)-(4-**methoxyphenylthio**)pyrrolidine 204072-61-7P, 1-(4-Butoxyphenylsulfonyl)-(2R)-carbomethoxy-(4S)-(3-pyridyloxy)pyrrolidine 204072-62-8P, 1-(4-Methoxyphenylsulfonyl)-(2R)-carbomethoxy-(4S)-azidopyrrolidine 204072-63-9P, 1-(4-Methoxyphenylsulfonyl)-(2R)-carbomethoxy-(4S)-aminopyrrolidine 204072-64-0P, 1-(4-Butoxyphenylsulfonyl)-(2R)-carbomethoxy-(4R)-methylsulfonyloxypyrrolidine 204072-65-1P, 1-(4-Butoxyphenylsulfonyl)-(2R)-carbomethoxy-(4S)-azidopyrrolidine 204072-66-2P, 1-(4-Butoxyphenylsulfonyl)-(2R)-carbomethoxy-(4S)-aminopyrrolidine 204072-67-3P, 1-(4-Methoxyphenylsulfonyl)-(2R)-carbomethoxy-(4S)-propylaminopyrrolidine

204072-68-4P, 1-(4-Methoxyphenylsulfonyl)-(2R)-carbomethoxy-(4S)-(hexylamino)pyrrolidine 204072-69-5P, 1-(4-Methoxyphenylsulfonyl)-(2R)-carbomethoxy-(4S)-(2-phenylethylamino)pyrrolidine 204072-70-8P, 1-(4-Methoxyphenylsulfonyl)-(2R)-carbomethoxy-(4S)-(N-butyl-N-hexylamino)pyrrolidine 204072-71-9P, 1-(4-Methoxyphenylsulfonyl)-(2R)-carbomethoxy-(4S)-[(methanesulfonyl)amino]pyrrolidine 204072-72-0P, 1-(4-Butoxyphenylsulfonyl)-(2R)-carbomethoxy-(4S)-[(methanesulfonyl)amino]pyrrolidine 204072-74-2P, 1-(4-Methoxyphenylsulfonyl)-(2R)-carbomethoxy-(4S)-[N-(3-pyridylmethyl)amino]pyrrolidine 204072-75-3P, 1-(4-Methoxyphenylsulfonyl)-(2R)-carbomethoxy-(4S)-[N-(3-pyridylmethyl)-N-(methanesulfonyl)amino]pyrrolidine 204072-76-4P, 1-(4-Methoxyphenylsulfonyl)-(2R)-carbomethoxy-(4S)-[bis(methanesulfonyl)amino]pyrrolidine 204072-77-5P, 1-(4-Methoxyphenylsulfonyl)-(2R)-carbomethoxy-(4S)-[N-(methanesulfonyl)-N-propylamino]pyrrolidine 204072-78-6P, 1-(4-Methoxyphenylsulfonyl)-(2R)-carbomethoxy-(4S)-[(4-methoxyphenylsulfonyl)amino]pyrrolidine 204072-79-7P, 1-(4-Methoxyphenylsulfonyl)-(2R)-carbomethoxy-(4S)-(hexanoylamino)pyrrolidine 204072-81-1P, 1-(4-Methoxyphenylsulfonyl)-(2R)-carbomethoxy-(4S)-[(methylcarbamoyl)amino]pyrrolidine 204072-82-2P, 1-(4-Methoxyphenylsulfonyl)-(2R)-carbomethoxy-(4S)-[N-(1-oxo-(2R)-benzyloxypropyl)amino]pyrrolidine 204072-83-3P, 1-(4-Methoxyphenylsulfonyl)-(2R)-carbomethoxy-(4S)-[N-(1-oxo-(2R)-benzyloxy-3-phenylpropyl)amino]pyrrolidine 204072-84-4P, 1-(4-Methoxyphenylsulfonyl)-(2R)-carbomethoxy-(4S)-[N-(1-oxo-(2R)-benzyloxypropyl)-N-propylamino]pyrrolidine 204072-85-5P, 1-(4-Methoxyphenylsulfonyl)-(2R)-carbomethoxy-(4S)-[N-(1-oxo-(2R)-hydroxypropyl)-N-propylamino]pyrrolidine 204072-86-6P, 1-(4-Methoxyphenylsulfonyl)-(2R)-carbomethoxy-(4S)-[N-(1-oxo-(2R)-benzyloxy-3-phenylpropyl)-N-propylamino]pyrrolidine 204072-87-7P, 1-(4-Methoxyphenylsulfonyl)-(2R)-carbomethoxy-(4S)-[N-(1-oxo-(2R)-hydroxy-3-phenylpropyl)-N-propylamino]pyrrolidine 204072-88-8P, 1-(4-Methoxyphenylsulfonyl)-(2R)-carbomethoxy-(4S)-(1-piperidyl)pyrrolidine 204072-89-9P, 1-(4-Butoxyphenylsulfonyl)-(2R)-carbomethoxy-(4S)-(1-piperidyl)pyrrolidine 204072-90-2P, 1-(4-Methoxyphenylsulfonyl)-(2R)-carbomethoxy-(4S)-(morpholino)pyrrolidine 204072-91-3P, 1-(4-Butoxyphenylsulfonyl)-(2R)-carbomethoxy-(4S)-(morpholino)pyrrolidine 204072-92-4P, 1-(4-Methoxyphenylsulfonyl)-(2R)-carbomethoxy-(4S)-(1,1-**dioxothiomorpholino**)pyrrolidine 204072-93-5P, 1-(4-Butoxyphenylsulfonyl)-(2R)-carbomethoxy-(4S)-(1,1-**dioxothiomorpholino**)pyrrolidine 204072-94-6P 204072-95-7P 204072-96-8P 204072-97-9P 204072-98-0P 204072-99-1P 204073-00-7P 204073-04-1P, 1-(4-Methoxyphenylsulfonyl)-(2R)-carbomethoxy-4,4-bis(**ethylthio**)pyrrolidine 537704-28-2P, 1-(4-Methoxyphenylsulfonyl)-(2R)-carbomethoxy-(4S)-[4-(1,1,3,3-tetramethylbutyl)phenoxy]pyrrolidine 537704-32-8P, 1-(4-Butoxyphenylsulfonyl)-(2R)-carbomethoxy-(4S)-[[(1-methyl-3-imidazolyl)sulfonyl]amino]pyrrolidine 537704-35-1P, 1-(4-Methoxyphenylsulfonyl)-(2R)-carbomethoxy-(4S)-(4-biphenylylamino)pyrrolidine 722550-48-3P, 1-(4-Methoxyphenylsulfonyl)-(2R)-carbomethoxy-(4R)-(methanesulfonyl)pyrrolidine 722550-49-4P, 1-[4-(2-Methoxyethyl)phenylsulfonyl]-(2R)-carbomethoxy-(4R)-hydroxypyrrolidine 722550-52-9P, 1-(4-Methoxyphenylsulfonyl)-(2R)-carbomethoxy-5-pyrrolidinone 722550-53-0P, 1-(4-Methoxyphenylsulfonyl)-(2R)-carboxy-5-pyrrolidinone 722550-54-1P, 1-(4-Methoxyphenylsulfonyl)-(2R)-(N-benzyloxycarboxamido)-5-pyrrolidinone
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; preparation of N-sulfonyl pyrrolidine-2-carbohydroxamic acid as **metalloprotease** inhibitors for treatment of restenosis)

IT 81669-70-7, **Metalloprotease**
RL: BSU (Biological study, unclassified); BIOL (Biological study)

(preparation of N-sulfonyl pyrrolidine-2-carbohydroxamic acid as **metalloprotease** inhibitors for treatment of restenosis)

IT 204072-55-9P, 1-(4-Phenoxyphenylsulfonyl)-(2R)-carbomethoxy-(4R)-hydroxypyrrolidine
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of N-sulfonyl pyrrolidine-2-carbohydroxamic acid as **metalloprotease** inhibitors for treatment of restenosis)

IT 204071-36-3P, 1-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-hydroxypyrrolidine 204071-38-5P, 1-(4-Methoxyphenylsulfonyl)-(2S)-(N-hydroxycarboxamido)-(4R)-hydroxypyrrolidine 204071-40-9P, 1-(4-Methoxyphenylsulfonyl)-(2S)-(N-hydroxycarboxamido)-(4S)-hydroxypyrrolidine 204071-42-1P, 1-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-methoxypyrrolidine 204071-43-2P, 1-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-(2-**benzothiazolylthio**)pyrrolidine 204071-44-3P, 1-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4R)-(2-**benzothiazolylthio**)pyrrolidine 204071-45-4P, 1-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-(1-methyl-2-**imidazolylthio**)pyrrolidine 204071-46-5P, 1-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4R)-(1-methyl-2-**imidazolylthio**)pyrrolidine 204071-47-6P, 1-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-phenoxypyrrolidine 204071-48-7P, 1-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-[4-(benzyloxy)phenoxy]pyrrolidine 204071-49-8P, 1-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-(3-phenylaminophenoxy)pyrrolidine 204071-50-1P, 1-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-(3-pyridinyloxy)pyrrolidine 204071-51-2P, 1-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-**phenylthiopyrrolidine** 204071-52-3P, 1-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-(4-**methoxyphenylthio**)pyrrolidine 204071-53-4P, 1-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-(3-**methoxyphenylthio**)pyrrolidine 204071-54-5P, 1-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4R)-ethoxymethoxypyrrolidine 204071-55-6P, 1-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4R)-benzyloxymethoxypyrrolidine 204071-56-7P, 1-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4R)-[(2-methoxyethoxy)methoxy]pyrrolidine 204071-57-8P, 1-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-**mercaptopyrrolidine** 204071-58-9P 204071-59-0P, 1-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4R)-4-hydroxy-4-ethylpyrrolidine 204071-60-3P, 1-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4R)-4-hydroxy-4-phenylpyrrolidine 204071-62-5P, 1-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-3,3-dimethyl-(4R)-hydroxypyrrolidine 204071-63-6P, 1-(4-Methylphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-hydroxypyrrolidine 204071-64-7P, 1-(3,4-Dimethoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4R)-hydroxypyrrolidine 204071-65-8P, 1-(2-Nitro-4-methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4R)-hydroxypyrrolidine 204071-66-9P, 1-(4-Butoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4R)-hydroxypyrrolidine 204071-67-0P, 1-(4-Butoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-hydroxypyrrolidine 204071-68-1P, 1-(4-Bromobenzenesulfonyl)-(2R)-(N-hydroxycarboxamido)-(4R)-hydroxypyrrolidine 204071-69-2P, 1-(2-Methyl-4-bromobenzenesulfonyl)-(2R)-(N-hydroxycarboxamido)-(4R)-hydroxypyrrolidine 204071-70-5P, 1-(2,4-Dichlorophenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4R)-hydroxypyrrolidine 204071-72-7P, 1-(4-Phenoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4R)-hydroxypyrrolidine 204071-73-8P,

1-(4-Isobutyloxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4R)-hydroxypyrrolidine 204071-74-9P, 1-(2-Methyl-4-bromophenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-(3-**methoxyphenylthio**)pyrrolidine 204071-75-0P, 1-(4-Butoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-(2-**benzothiazolylthio**)pyrrolidine 204071-76-1P, 1-(2-Nitro-4-methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-(2-**benzothiazolylthio**)pyrrolidine 204071-77-2P, 1-(4-Butoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-(4-**methoxyphenylthio**)pyrrolidine 204071-78-3P, 1-(4-Butoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-(3-pyridyloxy)pyrrolidine 204071-79-4P, 1-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-aminopyrrolidine 204071-81-8P, 1-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-propylaminopyrrolidine 204071-82-9P, 1-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-(hexylamino)pyrrolidine 204071-83-0P, 1-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-(2-phenylethylamino)pyrrolidine 204071-84-1P, 1-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-(N-butyl-N-hexylamino)pyrrolidine 204071-86-3P, 1-(4-Butoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-[(methanesulfonyl)amino]pyrrolidine 204071-88-5P, 1-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-[N-(3-pyridylmethyl)-N-(methanesulfonyl)amino]pyrrolidine 204071-89-6P, 1-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-[bis(methanesulfonyl)amino]pyrrolidine 204071-90-9P, 1-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-[N-(methanesulfonyl)-N-propylamino]pyrrolidine 204071-91-0P, 1-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-[(4-methoxyphenylsulfonyl)amino]pyrrolidine 204071-92-1P, 1-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-(hexanoylamino)pyrrolidine 204071-94-3P, 1-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-[(methylcarbamoyl)amino]pyrrolidine 204071-95-4P, 1-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-[N-(1-oxo-(2R)-benzyloxypropyl)amino]pyrrolidine 204071-96-5P, 1-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-[N-(1-oxo-(2R)-benzyloxy-3-phenylpropyl)amino]pyrrolidine 204071-98-7P, 1-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-[N-(1-oxo-(2R)-hydroxy-3-phenylpropyl)-N-propylamino]pyrrolidine 204071-99-8P, 1-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-(1-piperidyl)pyrrolidine 204072-00-4P, 1-(4-Butoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-(1-piperidyl)pyrrolidine 204072-01-5P, 1-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-(morpholino)pyrrolidine 204072-02-6P, 1-(4-Butoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-(morpholino)pyrrolidine 204072-03-7P, 1-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-(1,1-**dioxothiomorpholino**)pyrrolidine 204072-04-8P, 1-(4-Butoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-(1,1-**dioxothiomorpholino**)pyrrolidine 204072-05-9P 204072-06-0P 204072-07-1P 204072-08-2P 204072-09-3P 204072-10-6P 204072-11-7P 204072-14-0P, 1-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-4,4-bis(**ethylthio**)pyrrolidine 537704-26-0P, 1-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4R)-hydroxypyrrolidine 537704-29-3P, 1-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-[4-(1,1,3,3-tetramethylbutyl)phenoxy]pyrrolidine 537704-34-0P, 1-(4-Butoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-[[(1-methyl-3-imidazolyl)sulfonyl]amino]pyrrolidine 537704-36-2P, 1-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-(4-biphenylylamino)pyrrolidine 537704-43-1P, 1-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-[N-(1-oxo-(2R)-hydroxypropyl)-N-propylamino]pyrrolidine 722550-50-7P, 1-[4-(2-Methoxyethyl)phenylsulfonyl]-(2R)-(N-hydroxycarboxamido)-(4R)-

hydroxypyrrolidine 722550-51-8P, 1-(4-Methoxyphenylsulfonyl)-(2R)-hydroxycarboxamido-(4S)-[(methanesulfonyl)amino]pyrrolidine 722550-55-2P, 1-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-5-pyrrolidinone
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of N-sulfonyl pyrrolidine-2-carbohydroxamic acid as **metalloprotease** inhibitors for treatment of restenosis)

IT 60-56-0, 2-**Mercapto**-1-methylimidazole 65-85-0, Benzoic acid, reactions 74-88-4, Methyl iodide, reactions 75-08-1, **Ethanethiol** 77-71-4, 5,5-Dimethylhydantoin 98-58-8, 4-Bromobenzenesulfonyl chloride 98-59-9, p-Toluenesulfonyl chloride 98-68-0, 4-Methoxyphenylsulfonyl chloride 100-39-0, Benzyl bromide 100-46-9, Benzylamine, reactions 100-58-3, Phenylmagnesium bromide 101-18-8, 3-Hydroxydiphenylamine 103-16-2, 4-(Benzyloxy)phenol 108-95-2, Phenol, reactions 108-98-5, **Thiophenol**, reactions 109-00-2, 3-Hydroxypyridine 111-26-2, Hexylamine 111-30-8, Glutaric dialdehyde 122-78-1, Phenylacetaldehyde 123-38-6, Propionaldehyde, reactions 124-63-0, Methanesulfonyl chloride 140-66-9, 4-Octylphenol 142-61-0, Hexanoyl chloride 149-30-4, 2-**Mercaptobenzothiazole** 358-23-6 500-22-1, 3-Pyridinecarboxaldehyde 507-09-5, **Thioacetic** acid, reactions 616-04-6, 1-Methylhydantoin 624-83-9, Methyl isocyanate 696-63-9, 4-**Methoxythiophenol** 925-90-6, Ethylmagnesium bromide 1138-56-3, p-Butoxyphenylsulfonyl chloride 1499-56-5, trans-4-Hydroxy-L-proline methyl ester 1623-92-3, 4-Phenoxyphenylsulfonyl chloride 2051-62-9, 4-Biphenylyl chloride 2584-71-6, D-cis-4-Hydroxyproline 3188-13-4, Ethyl chloromethyl ether 3366-93-6, 1-Allylhydantoin 3587-60-8, Benzyl chloromethyl ether 3970-21-6, (2-Methoxyethoxy)methyl chloride 4042-36-8, (2R)-2-Carboxy-5-pyrrolidinone 5414-19-7, 2-Bromoethyl ether 6482-24-2, 2-Bromoethyl methyl ether 7617-67-6, Bis(2-bromoethyl) sulfone 15570-12-4, 3-**Methoxythiophenol** 16271-33-3, 2,4-Dichlorobenzenesulfonyl chloride 18092-54-1, 2-Nitro-4-methoxybenzenesulfonyl chloride 20312-36-1, L-3-Phenyllactic acid 23095-31-0, 3,4-Dimethoxyphenylsulfonyl chloride 33106-32-0, O-Benzyl-L-lactic acid 40856-73-3, (L)-5-Methylhydantoin 51212-37-4 81102-38-7, cis-4-Hydroxy-L-proline methyl ester 114676-47-0, cis-4-Hydroxy-D-proline methyl ester 139937-37-4, 2-Methyl-4-bromobenzenesulfonyl chloride 537704-27-1, Hydroxylamine monopotassium salt 537704-33-9
RL: RCT (Reactant); RACT (Reactant or reagent)
(reactant; preparation of N-sulfonyl pyrrolidine-2-carbohydroxamic acid as **metalloprotease** inhibitors for treatment of restenosis)

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DOCUMENT NUMBER: **141:38534**
TITLE: Preparation of aromatic sulfone hydroxamic acid **metalloprotease** inhibitors
INVENTOR(S): Barta, Thomas E.; Becker, Daniel P.; Bedell, Louis J.; Boehm, Terri L.; Carroll, Jeffrey N.; Decrescenzo, Gary A.; Fobian, Yvette M.; Freskos, John N.; Getman, Daniel P.; McDonald, Joseph J.; Li, Madeleine H.;

Hockerman, Susan L.; Howard, Susan C.; Kolodziej, Steve A.; Mischke, Deborah A.; Rico, Joseph G.; Stehle, Nathan W.; Tollefson, Michael B.; Vernier, William F.; Villamil, Clara I.

PATENT ASSIGNEE(S): Pharmacia Corporation, USA

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CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 5

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6750228	B1	20040615	US 2000-570731	20000512
US 2001014688	A1	20010816	US 1998-191129	19981113
US 2001039287	A1	20011108	US 1999-256948	19990224
CA 2372934	AA	20001123	CA 2000-2372934	20000515
WO 2000069821	A1	20001123	WO 2000-US6719	20000515
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1183239	A1	20020306	EP 2000-930088	20000515
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
BR 2000010562	A	20030610	BR 2000-10562	20000515
JP 2003520196	T2	20030702	JP 2000-618238	20000515
AU 766792	B2	20031023	AU 2000-47970	20000515
NZ 515217	A	20040430	NZ 2000-515217	20000515
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ZA 2001009006	A	20021202	ZA 2001-9006	20011031
NO 2001005543	A	20020110	NO 2001-5543	20011113
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PRIORITY APPLN. INFO.:

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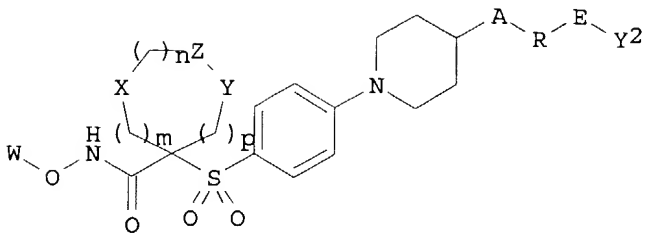
US 2000-570731	A	20000512
WO 2000-US6719	W	20000515
US 2001-989943	A3	20011121

OTHER SOURCE(S): MARPAT 141:38534

GI



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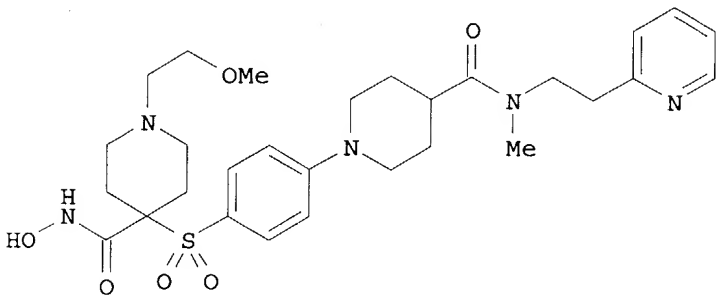

II

AB A treatment process is disclosed that comprises administering an effective amount of an aromatic sulfone hydroxamic acid I [W = H, cation, certain acyl or **thioacyl** groups; m, n, p = 0-2; (m+n+p) = 1 to 4; Z = (un)substituted NH; X, Y = (un)substituted CH2; A = bond, O, S, (un)substituted NH, COO, OCO, CH:CH, C.tplbond.C, N:N, NHNH, NHCOO, (un)substituted CONH, NHCO, etc.; R = alkylene, arylene, heteroarylene, etc., with provisos; E = bond, CONH, NHCO, CO, SO2, NHSO2, SO2NH, S, etc.; Y2 = absent, H, alkyl, alkoxy, aryl, aryloxy, heteroaryl, etc.] to a host having a condition associated with pathol. matrix **metalloprotease** (**MMP**) activity. I exhibit excellent inhibitory activity of one or more **MMP** enzymes, such as **MMP**-2, **MMP**-9 and **MMP**-13, while exhibiting substantially less inhibition of (at least) **MMP**-1 (biol. data given). Also disclosed are **metalloprotease** inhibitor compds. having such selective activities, processes for manufacture of such compds., and pharmaceutical compns. using such inhibitors. The compds. are potentially useful against a wide variety of conditions, notably as antiosteoarthritic, antiangiogenesis, and antitumor agents. Over 900 example compds. are listed, most with supporting phys. data, and many with synthetic details. E.g., a multi-step synthesis of the compound II.2HCl was given.

ED Entered STN: 16 Jun 2004

IC ICM A61K031-445
ICS C07D211-06

NCL 514316000; 514318000; 514328000; 514330000; 546189000; 546193000; 546220000; 546225000

CC 27-16 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 1, 7, 63

ST arom sulfone hydroxamic acid prepn matrix **metalloprotease** inhibitor; **MMP** inhibitor prepn hydroxamic acid pyran **thiopyran** piperidine; osteoarthritis arom sulfone hydroxamic acid prepn; antitumor arom sulfone hydroxamic acid prepn; angiogenesis arom sulfone hydroxamic acid prepn

IT Angiogenesis
Angiogenesis inhibitors
Anti-inflammatory agents

Antiarthritics
Antitumor agents
Drug delivery systems
Human
Neoplasm
Osteoarthritis
(preparation of aromatic sulfone hydroxamic acids as **metalloprotease** inhibitors)

IT Hydroxamic acids
Sulfones
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of aromatic sulfone hydroxamic acids as **metalloprotease** inhibitors)

IT 9001-12-1, **MMP**-1 141907-41-7, Matrix **metalloprotease** 146480-35-5, **MMP** 2 146480-36-6, **MMP** 9 175449-82-8, **MMP**-13
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(binding; preparation of aromatic sulfone hydroxamic acids as **metalloprotease** inhibitors)

IT 308822-81-3P 308822-82-4P 308822-86-8P 308822-95-9P 308823-05-4P 308824-05-7P 308824-24-0P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(drug candidate; preparation of aromatic sulfone hydroxamic acids as **metalloprotease** inhibitors)

IT 226390-98-3P 226391-00-0P 226391-03-3P 226391-36-2P 226391-57-7P
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RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(drug candidate; preparation of aromatic sulfone hydroxamic acids as **metalloprotease** inhibitors)

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RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU
(Therapeutic use); BIOL (Biological study); PREP (Preparation); USES
(Uses)
(drug candidate; preparation of aromatic sulfone hydroxamic acids as
metalloprotease inhibitors)

IT 308826-93-9P 308826-94-0P 308826-95-1P 308826-96-2P 308826-97-3P
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RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU

(Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(drug candidate; preparation of aromatic sulfone hydroxamic acids as **metalloprotease** inhibitors)

IT 308829-40-5P 308829-41-6P 308829-42-7P 308829-43-8P 308829-44-9P
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308832-77-1P 308832-78-2P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(drug candidate; preparation of aromatic sulfone hydroxamic acids as **metalloprotease** inhibitors)

IT 405-31-2P 4783-86-2P 81151-35-1P 84358-13-4P 113113-66-9P
138647-49-1P 142851-03-4P 162881-76-7P 180695-79-8P 188527-08-4P
192329-80-9P 192330-49-7P 193022-95-6P 195503-42-5P 226388-52-9P
226388-56-3P 226388-60-9P 226389-21-5P 226389-49-7DP, resin-bound
226389-52-2P 226391-07-7DP, resin-bound 226395-65-9P 226395-75-1P
226395-93-3P 226396-02-7P 226396-03-8P 226396-33-4P 226396-34-5P
226396-40-3P 226396-42-5P 226396-44-7P 226396-51-6P 226396-53-8P
226396-54-9P 226396-56-1P 226396-62-9P 226396-63-0P 226396-64-1P
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RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; preparation of aromatic sulfone hydroxamic acids as **metalloprotease** inhibitors)

IT 51-45-6, Histamine, reactions 62-53-3, Aniline, reactions 67-62-9, Methoxyamine 75-04-7, Ethylamine, reactions 78-81-9, Isobutylamine

90-04-0 95-51-2, 2-Chloroaniline 96-34-4, Methyl 2-chloroacetate
98-09-9, Benzenesulfonyl chloride 98-16-8, 3-(Trifluoromethyl)aniline
98-88-4, Benzoyl chloride 99-89-8, 4-Isopropylphenol 99-98-9,
N,N-Dimethyl-p-phenylenediamine 100-07-2, 4-Anisoyl chloride 100-39-0,
Benzyl bromide 100-46-9, Benzylamine, reactions 100-61-8,
N-Methylaniline, reactions 103-67-3, N-Benzylmethylamine 103-71-9,
Phenyl isocyanate, reactions 103-76-4, N-(2-Hydroxyethyl)piperazine
103-80-0, Phenylacetyl chloride 104-12-1, 4-Chlorophenyl isocyanate
104-81-4, 4-Methylbenzyl bromide 104-94-9 106-38-7, 4-Bromotoluene
106-96-7, Propargyl bromide 107-08-4, 1-Iodopropane 107-10-8,
1-Propylamine, reactions 108-00-9, N,N-Dimethylethylenediamine
108-42-9, 3-Chloroaniline 108-95-2, Phenol, reactions 108-98-5,
Thiophenol, reactions 109-00-2, 3-Hydroxypyridine 109-01-3,
1-Methylpiperazine 109-85-3, 2-Methoxyethylamine 109-89-7,
Diethylamine, reactions 109-90-0, Ethyl isocyanate 110-85-0,
Piperazine, reactions 110-89-4, Piperidine, reactions 110-91-8,
Morpholine, reactions 110-96-3, Diisobutylamine 111-49-9 111-95-5
122-04-3, 4-Nitrobenzoyl chloride 122-99-6, Ethylene glycol phenyl ether
123-75-1, Pyrrolidine, reactions 123-90-0, **Thiomorpholine**
124-02-7 124-40-3, Dimethylamine, reactions 141-43-5, Ethanolamine,
reactions 142-25-6, N,N,N'-Trimethylethylenediamine 150-76-5,
4-Methoxyphenol 156-87-6, 3-Amino-1-propanol 288-32-4, Imidazole,
reactions 288-88-0, 1H-1,2,4-Triazole 312-94-7, 2-
(Trifluoromethyl)benzoyl chloride 329-01-1, 3-(Trifluoromethyl)phenyl
isocyanate 329-15-7, 4-(Trifluoromethyl)benzoyl chloride 348-54-9,
2-Fluoroaniline 371-40-4, 4-Fluoroaniline 371-41-5, 4-Fluorophenol
371-42-6, 4-(Fluoro)**thiophenol** 372-19-0, 3-Fluoroaniline
393-52-2, 2-Fluorobenzoyl chloride 395-44-8, 2-(Trifluoromethyl)benzyl
bromide 402-23-3, 3-(Trifluoromethyl)benzyl bromide 402-45-9,
α,α,α-Trifluoro-p-cresol 403-43-0, 4-Fluorobenzoyl
chloride 404-71-7, 3-Fluorophenyl isocyanate 407-25-0, Trifluoroacetic
anhydride 421-83-0, Trifluoromethanesulfonyl chloride 455-14-1,
4-(Trifluoromethyl)aniline 459-46-1, 4-Fluorobenzyl bromide 461-82-5,
4-(Trifluoromethoxy)aniline 461-84-7, 4-(**Trifluoromethylthio**
)phenol 496-15-1, Indoline 498-94-2, Isonipecotic acid 504-24-5,
4-Aminopyridine 527-69-5, 2-Furoyl chloride 536-90-3 556-61-6,
Methyl **isothiocyanate** 591-54-8, 4-Aminopyrimidine 592-55-2,
2-Bromoethyl ethyl ether 616-45-5, 2-Pyrrolidinone 620-13-3,
3-Methylbenzyl bromide 622-95-7, 4-Chlorobenzyl bromide 625-43-4,
N-Methylisobutylamine 626-56-2, 3-Methylpiperidine 626-64-2,
4-Hydroxypyridine 627-37-2, N-Methylallylamine 658-46-8 694-05-3,
1,2,3,6-Tetrahydropyridine 753-90-2, 2,2,2-Trifluoroethylamine
777-44-6, 3-(Trifluoromethyl)benzenesulfonyl chloride 828-27-3,
p-(Trifluoromethoxy)phenol 874-60-2, 4-Toluoyl chloride 877-88-3,
3,5-Dimethoxybenzyl bromide 877-96-3, 1-[3-(Dimethylamino)propyl]piperaz
ine 929-06-6, 2-(2-Aminoethoxy)ethanol 933-88-0, 2-Toluoyl chloride
1008-91-9, 1-(4-Pyridyl)piperazine 1011-15-0, 1-(2-
Fluorophenyl)piperazine 1013-76-9, 1-(2,4-Dimethylphenyl)piperazine
1126-09-6, Ethyl isonipecotate 1195-45-5, 4-Fluorophenyl isocyanate
1423-27-4 1535-73-5, 3-(Trifluoromethoxy)aniline 1535-75-7,
2-(Trifluoromethoxy)aniline 1548-13-6, 4-(Trifluoromethyl)phenyl
isocyanate 1632-84-4, 4-(**Methylthio**)phenyl isocyanate
1645-65-4, 4-(Trifluoromethyl)phenyl **isothiocyanate** 1711-05-3,
3-Anisoyl chloride 1711-07-5, 3-Fluorobenzoyl chloride 1939-99-7,
α-Toluenesulfonyl chloride 2033-89-8, 3,4-Dimethoxyphenol
2038-57-5, Benzenepropanamine 2131-64-8, 4-(Dimethylamino)phenyl
isothiocyanate 2251-50-5, Pentafluorobenzoyl chloride
2251-65-2, 3-(Trifluoromethyl)benzoyl chloride 2252-63-3,
1-(4-Fluorophenyl)piperazine 2338-18-3 2516-47-4,
(Aminomethyl)cyclopropane 2836-04-6, N,N-Dimethyl-1,3-phenylenediamine

2971-79-1, Methyl isonipecotate 2991-42-6, 4-(Trifluoromethyl)benzenesulfonyl chloride 3173-56-6, Benzyl isocyanate 3202-33-3, 4-Phenoxypiperidine 3282-30-2, Pivaloyl chloride 3535-37-3, 3,4-Dimethoxybenzoyl chloride 3644-18-6, 1-[2-(Dimethylamino)ethyl]piperazine 3647-69-6, 4-(2-Chloroethyl)morpholine hydrochloride 3731-51-9, 2-(Aminomethyl)pyridine 3731-52-0, 3-(Aminomethyl)pyridine 3731-53-1, 4-(Aminomethyl)pyridine 4023-34-1, Cyclopropanecarbonyl chloride 4124-31-6, Trichloroacetic anhydride 4318-37-0, 1-Methylhomopiperazine 4318-42-7 4597-87-9, 2-(Methylamino)pyridine 4693-91-8, 4-Methoxyphenylacetyl chloride 4755-50-4, 4-(Dimethylamino)benzoyl chloride 4892-89-1, 1-(2-Morpholinoethyl)piperazine 5181-06-6, 1-(2-Methoxyphenyl)piperidine 5271-67-0, 2-**Thiophenecarbonyl** chloride 5292-43-3, tert-Butyl bromoacetate 5321-49-3, 1-(2-Phenylethyl)piperazine 5382-16-1, 4-Hydroxypiperidine 5414-19-7, Bis-(2-bromoethyl) ether 5638-76-6, 2-[2-(Methylamino)ethyl]pyridine 6269-89-2, 1-(4-Nitrophenyl)piperazine 6457-49-4, 4-(Hydroxymethyl)piperidine 6482-24-2, 2-Bromoethyl methyl ether 6485-55-8, cis-2,6-Dimethylmorpholine 6640-24-0, 1-(3-Chlorophenyl)piperazine 6711-48-4, 3,3'-Iminobis(N,N-dimethylpropylamine) 6723-30-4, O-(Tetrahydro-2H-pyran-2-yl)hydroxylamine 7357-67-7, 3-Morpholinopropyl chloride 7377-26-6, Methyl 4-(chlorocarbonyl)benzoate 7379-35-3, 4-Chloropyridine hydrochloride 10111-08-7, 2-Imidazolecarboxaldehyde 10400-19-8, Nicotinoyl chloride 13339-01-0, 1-(2-Ethoxyphenyl)piperazine 13349-82-1, 1-[2-(2-Hydroxyethoxy)ethyl]piperazine 13484-40-7, 1-(2-Methoxyethyl)piperazine 13889-98-0, 1-Acetylpiperazine 13961-36-9, 1-Allylpiperazine 14254-57-0, Isonicotinoyl chloride 14446-75-4, cis-3,5-Dimethylpiperidine 15268-31-2, 3-Pyridyl isocyanate 16413-26-6, 3-Cyanophenyl isocyanate 16744-98-2, 2-Fluorophenyl isocyanate 17201-43-3, 4-Cyanobenzyl bromide 17213-57-9, 3,5-Dimethoxybenzoyl chloride 17452-27-6 17739-45-6, 2-(2-Bromoethoxy)tetrahydro-2H-pyran 18880-04-1, 3,4-Dichlorobenzyl bromide 19853-09-9, 2-Phenylbenzyl bromide 20662-53-7 20980-22-7, 2-(1-Piperazinyl)pyrimidine 21043-40-3, 1-Cyclopentylpiperazine 21615-34-9, 2-Anisoyl chloride 21655-48-1, cis-2,6-Dimethylpiperazine 26389-60-6, N-Propylcyclopropanemethylamine 27129-86-8, 3,5-Dimethylbenzyl bromide 27374-25-0, [(1-Ethoxycyclopropyl)oxy]trimethylsilane 27757-85-3, 2-**Thiophenemethylamine** 30459-17-7, 1-[4-(Trifluoromethyl)phenyl]piperazine 32452-46-3, trans-3,5-Dimethylpiperidine 32459-62-4, 4-Ethoxyphenyl isocyanate 32813-24-4, 2-Piperidinoethyl **isothiocyanate** 33403-97-3, 4-(Ethylaminomethyl)pyridine 34803-66-2, 1-(2-Pyridyl)piperazine 34803-68-4, 1-(2-Pyrazinyl)piperazine 35161-71-8, N-Methylpropargylamine 35309-20-7, 3-Isocyanatopropionic acid 35386-24-4, 1-(2-Methoxyphenyl)piperazine 35730-09-7, 2,5-Difluorobenzoyl chloride 35794-11-7, 3,5-Dimethylpiperidine 35947-12-7, 1-(4-Methoxyphenyl)-2-methylpiperazine 36823-88-8, 4-(Trifluoromethoxy)benzoyl chloride 37517-81-0, Methyl malonyl chloride 38778-05-1, 4-(Phenoxy) **benzenethiol** 39512-50-0, 1-(2-Chlorophenyl)piperazine 39546-32-2, Isonipecotamide 39890-45-4, N-[2-(1-Piperazinyl)acetyl]pyrrolidine 40004-08-8, 1-(Ethoxycarbonylmethyl)piperazine 40172-95-0, 1-(2-Furoyl)piperazine 45597-00-0, cis-3,5-Dimethylmorpholine 49647-20-3, 4-Acetylphenyl isocyanate 50824-05-0, 4-(Trifluoromethoxy)benzyl bromide 51639-48-6 53460-46-1, 1,3,3-Trimethyl-6-azabicyclo[3.2.1]octane 54288-70-9, 4-Bromopiperidine hydrobromide 56346-57-7, 4-(4-Fluorobenzoyl)piperidine 56651-60-6, 4-Methoxybenzyl isocyanate 58315-38-1, N-[2-Nitro-4-(trifluoromethyl)phenyl]piperazine 58333-75-8, 4-(2-Methoxyphenyl)piperidine 63224-35-1, 2-Morpholinoethyl **isothiocyanate** 68337-15-5, 4-(1,2,4-Triazol-1-yl)phenol

68832-13-3 69628-75-7, 1-(1-Phenylethyl)piperazine 76362-12-4, 4-(4-Methoxybenzoyl)piperidine 76835-20-6, 1-(5-Chloro-2-methylphenyl)piperazine 79099-07-3 82911-69-1, N-(9-Fluorenylmethoxycarbonyloxy)succinimide 85118-01-0, 3,4-Difluorobenzyl bromide 85275-45-2 87394-63-6, 1-[3-(Trifluoromethyl)pyrid-2-yl]piperazine 103008-51-1, 2-(Trifluoromethoxy)benzenesulfonyl chloride 109384-19-2 115761-79-0, 1-(2,4-Difluorophenyl)piperazine 118708-88-6, 1-[4-(Trifluoromethyl)-2-pyridyl]piperazine 120104-92-9 132834-59-4, 1-[3-Chloro-5-(trifluoromethyl)pyrid-2-yl]piperazine 159689-88-0, 3-(Trifluoromethoxy)benzyl bromide 175277-80-2 179756-91-3, 1-[4-(Trifluoromethyl)-2-pyrimidyl]piperazine 226400-27-7 308830-98-0
RL: RCT (Reactant); RACT (Reactant or reagent)
(starting material; preparation of aromatic sulfone hydroxamic acids as **metalloprotease** inhibitors)

IT 308830-99-1 308831-00-7, 4-(3,5-Dimethylphenoxy)piperidine 308831-01-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(starting material; preparation of aromatic sulfone hydroxamic acids as **metalloprotease** inhibitors)

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Tang	2001	33	33	The International Jo	HCAPLUS
Woessner	1998		1	Matrix Metalloprotei	

L21 ANSWER 4 OF 28 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:991502 HCAPLUS
DOCUMENT NUMBER: **140:28052**
TITLE: Asymmetric synthesis of aminopyrrolidinones
INVENTOR(S): Waltermire, Robert E.; Savage, Scott A.; Campagna, Silvio; Magnus, Nicholas A.; Confalone, Pasquale N.; Yates, Matthew; Meloni, David J.
PATENT ASSIGNEE(S): Bristol-Myers Squibb Company, USA
SOURCE: PCT Int. Appl., 65 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
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WO 2003104220	A1	20031218	WO 2003-US7969	20030314
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003236401	A1	20031225	US 2003-389528	20030314
US 6770763	B2	20040803		

PRIORITY APPLN. INFO.: US 2002-387637P P 20020611
OTHER SOURCE(S): CASREACT 140:28052; MARPAT 140:28052
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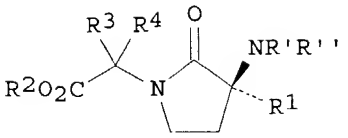

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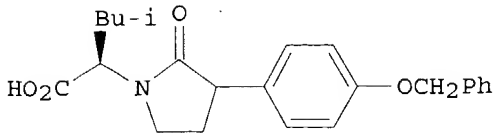
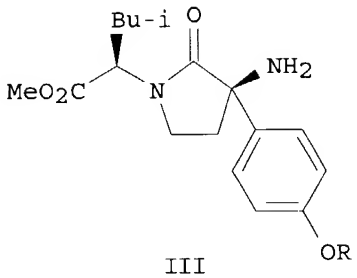


II



III

AB A novel process for the asym. synthesis of an aminopyrrolidinones I [R' is H, (cyclo)alkyl; R'' is a group R' or OH; R1 is substituted Ph or pyridyl; R2 is H, alkyl, Ph, benzyl; R3 is H, Q, (oxa)(aza)alk(en)(yn)ylene-Q, where Q is (un)substituted carbocyclyl; R4 is (oxa)(aza)alk(en)(yn)ylene-H] and corresponding aminoazetidinone, aminopiperidinone, and aminohexahydroazepinone analogs involves amination of corresponding pyrrolidinones or analogs. The products are useful as intermediates for **MMP** and TACE inhibitors. Thus, pyrrolidinone II was prepared by cyclocondensation of p-PhCH2OC6H4CH(CH2CHO)CO2Me with D-leucine Me ester hydrochloride. Amination of II with 1-chloro-1-nitrosocyclopentane, followed by catalytic hydrogenation in MeOH, mesylation, N-protection with p-tolualdehyde, and reaction with 4-(chlormethyl)-2-methylquinoline (R-Cl) afforded III (isolated as the HCl salt).

ED Entered STN: 21 Dec 2003

IC ICM C07D401-10
ICS C07D207-04

CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 7, 28

ST aminopyrrolidinone leucine deriv prepn inhibitor TACE **MMP**; pyrrolidinone amino leucine deriv prepn inhibitor TACE **MMP**

RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Kisfaludy	1984			US 4428938	HCAPLUS
Merck & Co Inc	1998			WO 9844797	HCAPLUS

L21 ANSWER 5 OF 28 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:875294 HCAPLUS
DOCUMENT NUMBER: **139:364955**
TITLE: Preparation of triaryl-oxy-aryl-spiro-pyrimidinetrione metalloproteinase inhibitors selective towards **MMP**-13
INVENTOR(S): Freeman-cook, Kevin Daniel; Noe, Mark Carl
PATENT ASSIGNEE(S): Pfizer Products Inc., USA
SOURCE: PCT Int. Appl., 92 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003091259	A1	20031106	WO 2003-IB1576	20030415
WO 2003091259	C1	20040212		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2003225056	A1	20031204	US 2003-423671	20030425
PRIORITY APPLN. INFO.:			US 2002-376157P P	20020426

OTHER SOURCE(S): MARPAT 139:364955
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The present invention relates to triaryl-oxy-aryl-spiro-pyrimidinetrione metalloproteinase inhibitors (shown as I; variables defined below; e.g. II) and to pharmaceutical compns. and methods of treating inflammation, cancer and other disorders. For I: ; ring X is a 5-7 membered heterocyclic ring; A is (C6-C10)aryl or (C1-C10)heteroaryl; Y = a bond, -O-, -S-, >C:O, >SO2, >S:O, -CH2O-, -OCH2-, -CH2S-, -SCH2-, -CH2SO-, -CH2SO2-, -SOCH2-, -SO2CH2-, >NR14, -[N(R14)]CH2-, -CH2[N(R14)]-, -CH2-, -CH:CH-, -C.tplbond.C-, -[N(R14)]SO2- and -SO2[N(R14)]-; B is (C6-C10)aryl, (C3-C7)cycloalkyl, (C1-C10)heterocyclyl and (C1-C10)heteroaryl; G is -R15(CR16R17)p-; p = 0-4; W is (C1-C4)alkoxy(C1-C4)alkyl, (C3-C7)cycloalkyl, (C6-C10)aryl, (C1-C10)heteroaryl and (C1-C10)heterocyclyl; addnl. details including provisos are given in the claims. General semiquant. statements are made about inhibition of metalloproteinases by I; no data is presented for specific examples of I; some I exhibit selectivity towards **MMP** -13 relative to other metalloproteinases but they are not identified. Although the methods of preparation are not claimed, example prepns. of 5 I are included.

ED Entered STN: 07 Nov 2003
IC ICM C07D487-10
ICS A61K031-505; A61P029-00; A61P037-00; A61P019-02; C07D239-00; C07D209-00
CC 28-16 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1, 63
ST triaryl oxy aryl spiro pyrimidinetrione prepn metalloproteinase inhibitor; **MMP13** selective metalloproteinase inhibitor triaryl oxy aryl spiro pyrimidinetrione; inflammation drug triaryl oxy aryl spiro pyrimidinetrione; cancer drug triaryl oxy aryl spiro pyrimidinetrione; pharmaceutical compn triaryl oxy aryl spiro pyrimidinetrione metalloproteinase inhibitor
IT Nervous system, disease

(central; preparation of triaryl-oxy-aryl-spiro-pyrimidinetrione metalloproteinase inhibitors selective towards **MMP**-13)

IT Immunity
Metabolism, animal
Reproduction, animal
(disorder; preparation of triaryl-oxy-aryl-spiro-pyrimidinetrione metalloproteinase inhibitors selective towards **MMP**-13)

IT Allergy
Allergy inhibitors
Anti-infective agents
Anti-inflammatory agents
Antitumor agents
Cardiovascular agents
Cardiovascular system, disease
Connective tissue, disease
Drug delivery systems
Eye, disease
Human
Immunomodulators
Infection
Inflammation
Kidney, disease
Liver, disease
Neoplasm
Nervous system agents
Respiratory tract, disease
Skin, disease
Stomach, disease
(preparation of triaryl-oxy-aryl-spiro-pyrimidinetrione metalloproteinase inhibitors selective towards **MMP**-13)

IT Spiro compounds
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of triaryl-oxy-aryl-spiro-pyrimidinetrione metalloproteinase inhibitors selective towards **MMP**-13)

IT 175449-82-8, **MMP**-13
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**MMP**-13, inhibitors; preparation of triaryl-oxy-aryl-spiro-pyrimidinetrione metalloproteinase inhibitors selective towards **MMP**-13)

IT 620971-38-2P, 1-[6-[4-[4-(4-Fluorophenyl)oxazol-2-yl]phenoxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620971-44-0P, 4-[2-[4-[[5-(6,8,10-Trioxo-1,7,9-triazaspiro[4.5]dec-1-yl)pyridin-2-yl]oxy]phenyl]oxazol-4-yl]benzonitrile 620971-47-3P, 3-[2-[4-[[5-(6,8,10-Trioxo-1,7,9-triazaspiro[4.5]dec-1-yl)pyridin-2-yl]oxy]phenyl]oxazol-4-yl]benzonitrile 620971-50-8P, 1-[6-[4-[4-(2-Fluorophenyl)oxazol-2-yl]phenoxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620971-52-0P, 1-[6-[4-[4-(3-Fluorophenyl)oxazol-2-yl]phenoxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(drug candidate; preparation of triaryl-oxy-aryl-spiro-pyrimidinetrione metalloproteinase inhibitors selective towards **MMP**-13)

IT 141907-41-7, Matrix metalloproteinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; preparation of triaryl-oxy-aryl-spiro-pyrimidinetrione metalloproteinase inhibitors selective towards **MMP**-13)

IT 109-64-8, 1,3-Dibromopropane 403-29-2, 2-Bromo-1-(4-fluorophenyl)ethanone 445-27-2, 1-(2-Fluorophenyl)ethanone 455-36-7, 1-(3-Fluorophenyl)ethanone 540-38-5, 4-Iodophenol 685-87-0, Diethyl bromomalonate 4548-45-2, 2-Chloro-5-nitropyridine 20099-89-2, 4-(2-Bromoacetyl)benzonitrile 50916-55-7, 3-(2-Bromoacetyl)benzonitrile
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of triaryl-oxy-aryl-spiro-pyrimidinetrione metalloproteinase inhibitors selective towards **MMP**-13)

IT 127426-15-7P, 4-(2-Fluorophenyl)oxazole 620633-04-7P, 4-(4-Fluorophenyl)oxazole 620971-39-3P, 1-[6-[4-[4-(4-Fluorophenyl)oxazol-2-yl]phenoxy]pyridin-3-yl]pyrrolidine-2,2-dicarboxylic acid diethyl ester 620971-40-6P 620971-41-7P, 2-(4-Iodophenoxy)-5-nitropyridine 620971-42-8P, [6-(4-Iodophenoxy)pyridin-3-yl]amine 620971-43-9P 620971-45-1P, 1-[6-[4-[4-(4-Cyanophenyl)oxazol-2-yl]phenoxy]pyridin-3-yl]pyrrolidine-2,2-dicarboxylic acid diethyl ester 620971-46-2P, 4-(Oxazol-4-yl)benzonitrile 620971-48-4P, 1-[6-[4-[4-(3-Cyanophenyl)oxazol-2-yl]phenoxy]pyridin-3-yl]pyrrolidine-2,2-dicarboxylic acid diethyl ester 620971-49-5P, 3-(Oxazol-4-yl)benzonitrile 620971-51-9P, 1-[6-[4-[4-(2-Fluorophenyl)oxazol-2-yl]phenoxy]pyridin-3-yl]pyrrolidine-2,2-dicarboxylic acid diethyl ester 620971-53-1P, 1-[6-[4-[4-(3-Fluorophenyl)oxazol-2-yl]phenoxy]pyridin-3-yl]pyrrolidine-2,2-dicarboxylic acid diethyl ester 620971-54-2P, 4-(3-Fluorophenyl)oxazole
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of triaryl-oxy-aryl-spiro-pyrimidinetrione metalloproteinase inhibitors selective towards **MMP**-13)

RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Blagg, J	2001			WO 0112611 A	HCAPLUS
Scott, B	2002			WO 0234753 A	HCAPLUS

L21 ANSWER 6 OF 28 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:875293 HCAPLUS
DOCUMENT NUMBER: **139:364954**
TITLE: Preparation of N-substituted-heteroaryloxy-aryl-spiro-pyrimidinetrione metalloproteinase inhibitors selective towards **MMP**-13
INVENTOR(S): Noe, Mark Carl; Freeman-cook, Kevin Daniel
PATENT ASSIGNEE(S): Pfizer Products Inc., USA
SOURCE: PCT Int. Appl., 86 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003091258	A1	20031106	WO 2003-IB1508	20030415

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,

FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
US 2004010141 A1 20040115 US 2003-423779 20030425
PRIORITY APPLN. INFO.: US 2002-376159P P 20020426
OTHER SOURCE(S): MARPAT 139:364954
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The present invention relates to N-substituted-heteroaryloxy-aryl-spiro-pyrimidine-2,4,6-trione metalloproteinase inhibitors (shown as I; variables defined below; e.g. II) and to pharmaceutical compns. and methods of treating inflammation, cancer and other disorders. For I: ; ring X is a 5-7 membered heterocyclic ring; A is (C6-C10)aryl or (C2-C10)heteroaryl; Y = a bond, -O-, -S-, >C:O, >SO2, >S:O, -CH2O-, -OCH2-, -CH2S-, -SCH2-, -CH2SO-, -CH2SO2-, -SOCH2-, -SO2CH2-, >NR14, -[N(R14)]CH2-, -CH2[N(R14)]-, -CH2-, -CH:CH-, -C.tplbond.C-, -[N(R14)]SO2- and -SO2[N(R14)]-; B is a heterocyclyl containing at least one N atom; wherein one ring N atom of B is bonded to one C atom of G; G is (C1-C6)alkyl or R15-(CR16R17)p-; p = 0-4; addnl. details including provisos are given in the claims. General semiquant. statements are made about inhibition of metalloproteinases by I; no data is presented for specific examples of I; some I exhibit selectivity towards **MMP**-13 relative to other metalloproteinases but they are not identified. Although the methods of preparation are not claimed, example prepns. of 4 I are included.

ED Entered STN: 07 Nov 2003

IC ICM C07D487-10
ICS A61K031-505; A61P037-00; A61P029-00; A61P019-02; C07D239-00; C07D209-00

CC 28-16 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1, 63

ST heteroaryloxy aryl spiro pyrimidinetrione prepn metalloproteinase inhibitor; **MMP13** selective metalloproteinase inhibitor heteroaryloxy aryl spiro pyrimidinetrione; cancer drug heteroaryloxy aryl spiro pyrimidinetrione; inflammation drug heteroaryloxy aryl spiro pyrimidinetrione; pharmaceutical compn heteroaryloxy aryl spiro pyrimidinetrione metalloproteinase inhibitor

IT Nervous system, disease
(central; preparation of N-substituted-heteroaryloxy-aryl-spiro-pyrimidinetrione metalloproteinase inhibitors selective towards **MMP**-13)

IT Immunity
Metabolism, animal
Reproduction, animal
(disorder; preparation of N-substituted-heteroaryloxy-aryl-spiro-pyrimidinetrione metalloproteinase inhibitors selective towards **MMP**-13)

IT Allergy
Allergy inhibitors
Anti-infective agents
Anti-inflammatory agents
Antitumor agents
Cardiovascular agents
Cardiovascular system, disease
Connective tissue, disease
Drug delivery systems
Eye, disease

Human
Immunomodulators
Infection
Inflammation
Kidney, disease
Liver, disease
Neoplasm
Nervous system agents
Respiratory tract, disease
Skin, disease
Stomach, disease
(preparation of N-substituted-heteroaryloxy-aryl-spiro-pyrimidinetrione metalloproteinase inhibitors selective towards **MMP**-13)

IT Spiro compounds
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of N-substituted-heteroaryloxy-aryl-spiro-pyrimidinetrione metalloproteinase inhibitors selective towards **MMP**-13)

IT 175449-82-8, **MMP**-13
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**MMP**-13, inhibitors; preparation of N-substituted-heteroaryloxy-aryl-spiro-pyrimidinetrione metalloproteinase inhibitors selective towards **MMP**-13)

IT 620965-06-2P, 1-[6-[[1-(4-Fluorophenyl)-1H-indazol-5-yl]oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620965-13-1P, 4-[5-[[5-(6,8,10-Trioxo-1,7,9-triazaspiro[4.5]dec-1-yl)pyridin-2-yl]oxy]indazol-1-yl]benzonitrile 620965-19-7P, 1-[6-[[1-(Pyridin-3-yl)-1H-indazol-5-yl]oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620965-26-6P, 1-[6-[(1-Methyl-1H-indazol-5-yl)oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620965-33-5P, 1-[6-[(1-Isopropyl-1H-indazol-5-yl)oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620965-35-7P, 1-[6-[(2-Isopropyl-2H-indazol-5-yl)oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620965-36-8P, 4-[5-[[5-(6,8,10-Trioxo-1,7,9-triazaspiro[4.5]dec-1-yl)pyridin-2-yl]oxy]indazol-2-yl]benzonitrile 620965-38-0P, 1-[6-[[2-(2-Hydroxyethyl)-1-oxo-2,3-dihydro-1H-isoindol-5-yl]oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620965-39-1P, 1-[6-[[2-(2-Ethoxyethyl)-1-oxo-2,3-dihydro-1H-isoindol-5-yl]oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620965-40-4P, 1-[6-[[2-(4-Fluorophenyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620965-41-5P, 1-[6-[[1-(4-Fluorophenyl)-1,2,3,4-tetrahydroquinolin-6-yl]oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620965-42-6P, 1-[6-[[1-(4-Fluorophenyl)-2,3-dihydro-1H-indol-5-yl]oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620965-43-7P, 1-[6-[[2-(Pyridin-3-yl)-2H-indazol-5-yl]oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620965-44-8P, 1-[6-[[2-(4-Fluorophenyl)-2,3-dihydro-1H-isoindol-5-yl]oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620965-45-9P, 1-[6-[[1-(Pyridin-3-yl)-2,3-dihydro-1H-indol-5-yl]oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620965-46-0P, 1-[6-[[2-(4-Fluorophenyl)-2H-indazol-5-yl]oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620965-47-1P, 1-[6-[[1-(4-Fluorophenyl)-2,3,4,5-tetrahydro-1H-benzo[b]azepin-7-yl]oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620965-48-2P, 1-[6-[[1-(4-Fluorophenyl)-1H-benzimidazol-5-yl]oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620965-49-3P, 6-[7-[[5-(6,8,10-Trioxo-1,7,9-triazaspiro[4.5]dec-1-yl)pyridin-2-yl]oxy]-2,3,4,5-tetrahydrobenzo[b]azepin-1-yl]nicotinonitrile 620965-50-6P,

6-[5-[[5-(6,8,10-Trioxo-1,7,9-triazaspiro[4.5]dec-1-yl)pyridin-2-yl]oxy]-2,3-dihydroindol-1-yl]nicotinonitrile 620965-51-7P, 1-[6-[[2-(Pyridin-3-yl)-2,3-dihydro-1H-isoindol-5-yl]oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620965-52-8P, 6-[6-[[5-(6,8,10-Trioxo-1,7,9-triazaspiro[4.5]dec-1-yl)pyridin-2-yl]oxy]-3,4-dihydro-2H-quinolin-1-yl]nicotinonitrile 620965-53-9P, 1-[6-[[1-(Pyridin-4-yl)-2,3,4,5-tetrahydro-1H-benzo[b]azepin-7-yl]oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620965-54-0P, 1-[6-[[1-(Pyridin-3-yl)-2,3,4,5-tetrahydro-1H-benzo[b]azepin-7-yl]oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620965-55-1P, 6-[6-[[5-(6,8,10-Trioxo-1,7,9-triazaspiro[4.5]dec-1-yl)pyridin-2-yl]oxy]-3,4-dihydro-1H-isoquinolin-2-yl]nicotinonitrile 620965-56-2P, 6-[5-[[5-(6,8,10-Trioxo-1,7,9-triazaspiro[4.5]dec-1-yl)pyridin-2-yl]oxy]-1,3-dihydroisoindol-2-yl]nicotinonitrile 620965-57-3P, 6-[5-[[5-(6,8,10-Trioxo-1,7,9-triazaspiro[4.5]dec-1-yl)pyridin-2-yl]oxy]indazol-1-yl]nicotinonitrile 620965-58-4P, 6-[5-[[5-(6,8,10-Trioxo-1,7,9-triazaspiro[4.5]dec-1-yl)pyridin-2-yl]oxy]indazol-2-yl]nicotinonitrile 620965-59-5P, 1-[6-[[2-(Pyridin-4-yl)-2,3-dihydro-1H-isoindol-5-yl]oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620965-60-8P, 1-[6-[[1-(Pyridin-4-yl)-1H-benzimidazol-5-yl]oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620965-61-9P, 1-[6-[[2-(Pyridin-4-yl)-1,2,3,4-tetrahydroisoquinolin-6-yl]oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620965-62-0P, 1-[6-[[2-(Pyridin-3-yl)-1,2,3,4-tetrahydroisoquinolin-6-yl]oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620965-63-1P, 1-[6-[[1-(Pyridin-4-yl)-2,3-dihydro-1H-indol-5-yl]oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620965-64-2P, 1-[6-[[1-(Pyridin-4-yl)-1H-indazol-5-yl]oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620965-65-3P, 1-[6-[[1-(Pyridin-3-yl)-1H-benzimidazol-5-yl]oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620965-66-4P, 1-[6-[[1-(Pyridin-4-yl)-1,2,3,4-tetrahydroquinolin-6-yl]oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620965-67-5P, 1-[6-[[2-(Pyridin-4-yl)-2H-indazol-5-yl]oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620965-68-6P, 1-[6-[[1-(Pyridin-3-yl)-1,2,3,4-tetrahydroquinolin-6-yl]oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620965-69-7P, 1-[6-[[2-(p-Tolyl)-2H-indazol-5-yl]oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620965-70-0P, 1-[6-[[2-(p-Tolyl)-2,3-dihydro-1H-isoindol-5-yl]oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620965-71-1P, 1-[6-[[2-(4-Chlorophenyl)-2H-indazol-5-yl]oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620965-72-2P, 1-[6-[[2-(4-Chlorophenyl)-2,3-dihydro-1H-isoindol-5-yl]oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620965-73-3P, 1-[6-[[2-(Pyridin-2-yl)-2H-indazol-5-yl]oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620965-74-4P, 1-[6-[[2-(Pyridin-2-yl)-2,3-dihydro-1H-isoindol-5-yl]oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620965-75-5P, 1-[6-[[2-(3-Methoxypropyl)-2H-indazol-5-yl]oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620965-76-6P, 1-[6-[[2-(Pyridazin-3-yl)-2H-indazol-5-yl]oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620965-77-7P, 1-[6-[(1-Isopropyl-2,3-dihydro-1H-indol-5-yl)oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620965-78-8P, 1-[6-[(1-Isopropyl-1H-benzimidazol-5-yl)oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620965-79-9P, 1-[6-[(2-Isopropyl-2,3-dihydro-1H-isoindol-5-yl)oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620965-80-2P, 1-[6-[[2-(Pyridin-2-yl)-1,2,3,4-tetrahydroisoquinolin-6-yl]oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620965-81-3P, 1-[6-[[2-(Pyridazin-3-yl)-1,2,3,4-tetrahydroisoquinolin-6-yl]oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620965-82-4P,

1-[6-[(2-Isopropyl-1,2,3,4-tetrahydroisoquinolin-6-yl)oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620965-83-5P, 1-[6-[[2-(Pyridazin-3-yl)-2,3-dihydro-1H-isoindol-5-yl]oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620965-84-6P, 1-[6-[[2-(3-Methoxypropyl)-2,3-dihydro-1H-isoindol-5-yl]oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620965-85-7P, 1-[6-[[2-(3-Methoxypropyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620965-86-8P, 1-[6-[[2-(4-Methoxyphenyl)-2H-indazol-5-yl]oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620965-87-9P, 1-[6-[(1-Isopropyl-1,2,3,4-tetrahydroquinolin-6-yl)oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620965-88-0P, 1-[6-[[1-(3-Methoxypropyl)-1,2,3,4-tetrahydroquinolin-6-yl]oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620965-89-1P, 1-[6-[[1-(Pyridin-2-yl)-2,3,4,5-tetrahydro-1H-benzo[b]azepin-7-yl]oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620965-90-4P, 1-[6-[[1-(Pyridazin-3-yl)-2,3,4,5-tetrahydro-1H-benzo[b]azepin-7-yl]oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620965-91-5P, 1-[6-[(1-Isopropyl-2,3,4,5-tetrahydro-1H-benzo[b]azepin-7-yl)oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620965-92-6P, 1-[6-[[2-(p-Tolyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620965-93-7P, 1-[6-[[1-(4-Methoxyphenyl)-2,3,4,5-tetrahydro-1H-benzo[b]azepin-7-yl]oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620965-94-8P, 1-[6-[[2-(4-Chlorophenyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620965-95-9P, 4-[6-[[5-(6,8,10-Trioxo-1,7,9-triazaspiro[4.5]dec-1-yl)pyridin-2-yl]oxy]-3,4-dihydro-1H-isoquinolin-2-yl]benzonitrile 620965-96-0P, 4-[5-[[5-(6,8,10-Trioxo-1,7,9-triazaspiro[4.5]dec-1-yl)pyridin-2-yl]oxy]-2,3-dihydroindol-1-yl]benzonitrile 620965-97-1P, 1-[6-[[1-(4-Methoxyphenyl)-1H-benzimidazol-5-yl]oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620965-98-2P, 1-[6-[[2-(4-Methoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620965-99-3P, 4-[6-[[5-(6,8,10-Trioxo-1,7,9-triazaspiro[4.5]dec-1-yl)pyridin-2-yl]oxy]-3,4-dihydro-2H-quinolin-1-yl]benzonitrile 620966-00-9P, 1-[6-[[1-(4-Methoxyphenyl)-1,2,3,4-tetrahydroquinolin-6-yl]oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620966-01-0P, 4-[7-[[5-(6,8,10-Trioxo-1,7,9-triazaspiro[4.5]dec-1-yl)pyridin-2-yl]oxy]-2,3,4,5-tetrahydrobenzo[b]azepin-1-yl]benzonitrile 620966-02-1P, 4-[5-[[5-(6,8,10-Trioxo-1,7,9-triazaspiro[4.5]dec-1-yl)pyridin-2-yl]oxy]-1,3-dihydroisoindol-2-yl]benzonitrile 620966-03-2P, 1-[6-[[1-(4-Chlorophenyl)-1,2,3,4-tetrahydroquinolin-6-yl]oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620966-04-3P, 1-[6-[[1-(p-Tolyl)-1,2,3,4-tetrahydroquinolin-6-yl]oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620966-05-4P, 4-[5-[[5-(6,8,10-Trioxo-1,7,9-triazaspiro[4.5]dec-1-yl)pyridin-2-yl]oxy]benzimidazol-1-yl]benzonitrile 620966-06-5P, 1-[6-[[1-(3-Methoxypropyl)-2,3,4,5-tetrahydro-1H-benzo[b]azepin-7-yl]oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620966-07-6P, 1-[6-[[1-(4-Chlorophenyl)-2,3,4,5-tetrahydro-1H-benzo[b]azepin-7-yl]oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620966-08-7P, 1-[6-[[1-(p-Tolyl)-2,3,4,5-tetrahydro-1H-benzo[b]azepin-7-yl]oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620966-09-8P, 1-[6-[[2-(4-Methoxyphenyl)-2,3-dihydro-1H-isoindol-5-yl]oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620966-10-1P, 1-[6-[[1-(Pyridazin-3-yl)-1,2,3,4-tetrahydroquinolin-6-yl]oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620966-11-2P, 1-[6-[[1-(Pyridin-2-yl)-1,2,3,4-tetrahydroquinolin-6-yl]oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620966-12-3P,

1-[6-[[1-(p-Tolyl)-1H-indazol-5-yl]oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620966-13-4P, 1-[6-[[1-(4-Methoxyphenyl)-2,3-dihydro-1H-indol-5-yl]oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620966-14-5P, 1-[6-[[1-(Pyridazin-3-yl)-1H-benzimidazol-5-yl]oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620966-15-6P, 1-[6-[[1-(Pyridazin-3-yl)-2,3-dihydro-1H-indol-5-yl]oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620966-16-7P, 1-[6-[[1-(Pyridazin-3-yl)-1H-indazol-5-yl]oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620966-17-8P, 1-[6-[[1-(Pyridin-2-yl)-1H-benzimidazol-5-yl]oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620966-18-9P, 1-[6-[[1-(Pyridin-2-yl)-2,3-dihydro-1H-indol-5-yl]oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620966-19-0P, 1-[6-[[1-(Pyridin-2-yl)-1H-indazol-5-yl]oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620966-20-3P, 1-[6-[[1-(4-Methoxyphenyl)-1H-indazol-5-yl]oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620966-21-4P, 1-[6-[[1-(4-Chlorophenyl)-1H-benzimidazol-5-yl]oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620966-22-5P, 1-[6-[[1-(3-Methoxypropyl)-1H-benzimidazol-5-yl]oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620966-23-6P, 1-[6-[[1-(3-Methoxypropyl)-2,3-dihydro-1H-indol-5-yl]oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620966-24-7P, 1-[6-[[1-(3-Methoxypropyl)-1H-indazol-5-yl]oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620966-25-8P, 1-[6-[[1-(4-Chlorophenyl)-2,3-dihydro-1H-indol-5-yl]oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620966-26-9P, 1-[6-[[1-(4-Chlorophenyl)-1H-indazol-5-yl]oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620966-27-0P, 1-[6-[[1-(p-Tolyl)-1H-benzimidazol-5-yl]oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione 620966-28-1P, 1-[6-[[1-(p-Tolyl)-2,3-dihydro-1H-indol-5-yl]oxy]pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-6,8,10-trione
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(drug candidate; preparation of N-substituted-heteroaryloxy-aryl-spiro-pyrimidinetrione metalloproteinase inhibitors selective towards **MMP**-13)

IT 141907-41-7, Matrix metalloproteinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; preparation of N-substituted-heteroaryloxy-aryl-spiro-pyrimidinetrione metalloproteinase inhibitors selective towards **MMP**-13)

IT 108-39-4, m-Cresol, reactions 109-64-8, 1,3-Dibromopropane 685-87-0, Diethyl bromomalonate 1692-25-7, (3-Pyridyl)boronic acid 1765-93-1, 4-Fluorophenylboronic acid 4548-45-2, 2-Chloro-5-nitropyridine 126747-14-6, 4-Cyanophenylboronic acid
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of N-substituted-heteroaryloxy-aryl-spiro-pyrimidinetrione metalloproteinase inhibitors selective towards **MMP**-13)

IT 620965-07-3P, 1-[6-[[1-(4-Fluorophenyl)-1H-indazol-5-yl]oxy]pyridin-3-yl]pyrrolidine-2,2-dicarboxylic acid diethyl ester 620965-08-4P, 2-[[6-[[1-(4-Fluorophenyl)-1H-indazol-5-yl]oxy]pyridin-3-yl]amino]malonic acid diethyl ester 620965-09-5P, [6-[[1-(4-Fluorophenyl)-1H-indazol-5-yl]oxy]pyridin-3-yl]amine 620965-10-8P, 1-(4-Fluorophenyl)-5-[(5-nitropyridin-2-yl)oxy]-1H-indazole 620965-11-9P, 5-[(5-Nitropyridin-2-yl)oxy]-1H-indazole 620965-12-0P, [2-Methyl-4-[(5-nitropyridin-2-yl)oxy]phenyl]amine 620965-14-2P, 1-[6-[[1-(4-Cyanophenyl)-1H-indazol-5-yl]oxy]pyridin-3-yl]pyrrolidine-2,2-dicarboxylic acid diethyl ester 620965-15-3P, 2-[[6-[[1-(4-Cyanophenyl)-1H-indazol-5-yl]oxy]pyridin-3-yl]amino]malonic acid diethyl ester 620965-16-4P, 4-[5-[(5-Aminopyridin-

2-yl)oxy]indazol-1-yl]benzonitrile 620965-18-6P, 4-[5-[(5-Nitropyridin-2-yl)oxy]indazol-1-yl]benzonitrile 620965-20-0P, 1-[6-[[1-(Pyridin-3-yl)-1H-indazol-5-yl]oxy]pyridin-3-yl]pyrrolidine-2,2-dicarboxylic acid diethyl ester 620965-21-1P, 2-[[6-[[1-(Pyridin-3-yl)-1H-indazol-5-yl]oxy]pyridin-3-yl]amino]malonic acid diethyl ester 620965-23-3P, 5-[(5-Aminopyridin-2-yl)oxy]-1-(pyridin-3-yl)-1H-indazole 620965-24-4P, 5-[(5-Nitropyridin-2-yl)oxy]-1-(pyridin-3-yl)-1H-indazole 620965-27-7P, 1-[6-[(1-Methyl-1H-indazol-5-yl)oxy]pyridin-3-yl]pyrrolidine-2,2-dicarboxylic acid diethyl ester 620965-29-9P, 2-[[6-[(1-Methyl-1H-indazol-5-yl)oxy]pyridin-3-yl]amino]malonic acid diethyl ester 620965-30-2P, 5-[(5-Aminopyridin-2-yl)oxy]-1-methyl-1H-indazole 620965-31-3P, 5-[(5-Nitropyridin-2-yl)oxy]-1-methyl-1H-indazole
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of N-substituted-heteroaryloxy-aryl-spiro-pyrimidinetrione metalloproteinase inhibitors selective towards **MMP**-13)

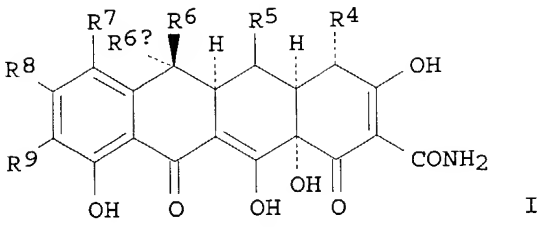
RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Blagg, J	2001			WO 0112611 A	HCAPLUS
Scott, B	2002			WO 0234753 A	HCAPLUS

L21 ANSWER 7 OF 28 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:818139 HCAPLUS
DOCUMENT NUMBER: **139:307637**
TITLE: Synthesis and phytotoxicity of 4-dedimethylaminotetracycline derivatives
INVENTOR(S): Ashley, Robert A.; Hlavka, Joseph J.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 37 pp., Cont.-in-part of U.S. Ser. No. 911,861.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2003195174	A1	20031016	US 2002-274841		20021018
US 6506740	B1	20030114	US 2000-573654		20000518
US 2002160987	A1	20021031	US 2001-911861		20010724
US 6638922	B2	20031028			
PRIORITY APPLN. INFO.:			US 1998-195013	B2	19981118
			US 2000-479604	B2	20000107
			US 2000-573654	A2	20000518
			US 2001-911861	A2	20010724
			US 1998-108948P	P	19981118

OTHER SOURCE(S): MARPAT 139:307637
GI



I

AB The 4-dedimethylaminotetracycline derivs., such as I [R4 = NOH, N-NH-alkyl, NH-alkyl; R5, R6 = H, OH; R6a = H, Me; R7 = H, (un)substituted amino, NO2, halogen, S(C=S)OEt, N3, acylamino, N2+, CN, OH; R9 = H, (un)substituted amino, NO2, N3, acylamino, OH, S(C=S)OEt, halogen, N2+, RCH(NH2)CO; R = H, alkyl; R8 = H, halogen], and their pharmaceutically acceptable salts were prepared and assayed for their phototoxicity using BALB/c 3T3 (CCL-163) cells. These tetracycline derivs. are claimed for use in the treatment of disorders involving excessive collagen destruction, excessive MT-**MMP** enzyme activity, excessive TNF activity, excessive nitric oxide activity, excessive IL-1 activity, excessive elastase activity, excessive loss of bone d., excessive protein degradation, excessive muscle wasting, excessive glycosylation of collagen, excessive COX-2 activity, insufficient bone protein synthesis, insufficient interleukin-10 production, excessive phospholipase A2 activity, as well as for treatment of abdominal aortic aneurysm, ulceration of the cornea, periodontal disease, diabetes, diabetes mellitus, scleroderma, progeria, cancer, graft vs. host disease, disease of depressed bone marrow function, thrombocytopenia, prosthetic joint loosening, spondyloarthropathies, osteoporosis, Paget's disease, autoimmune disease, systemic lupus erythematosus and connective tissue disease. 855These tetracyclines may also be used for treatment of inflammatory conditions, such as inflammatory bowel disease, arthritis, osteoarthritis, rheumatoid arthritis, pancreatitis, nephritis, glomerulonephritis, sepsis, septic shock, lipopolysaccharide endotoxin shock, multisystem organ failure, psoriasis, lung diseases, such as ARDS, cystic fibrosis, emphysema or acute lung injury resulting from inhalation of toxicants, renal diseases, such as chronic or acute renal failure, nephritis or glomerulonephritis, neurodegenerative diseases, such as Alzheimer's disease, Guillain-Barre Syndrome, Krabbe's disease, adrenoleukodystrophy, Parkinson's disease, Huntington's disease, multiple sclerosis, amyotrophic lateral sclerosis, and spongiform encephalopathy. Thus, I (R4,R5,R6,R8,R9 = H; R6a = Me; R7 = NO2) was prepared starting from I (R4,R5,R6,R7,R8,R9 = H; R6a = Me) via nitration.

ED Entered STN: 17 Oct 2003

IC ICM A61K031-65
ICS C07C237-26

NCL 514152000; 552204000

CC 26-6 (Biomolecules and Their Synthetic Analogs)
Section cross-reference(s): 1, 63

L21 ANSWER 8 OF 28 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:435318 HCAPLUS

DOCUMENT NUMBER: **139:22213**

TITLE: Preparation of substituted cyclic amines as **metalloprotease** inhibitors

INVENTOR(S): Natchus, Michael George; De, Biswanath; Pikul, Stanislaw; Almstead, Neil Gregory; Bookland, Roger Gunnard; Taiwo, Yetunde Olabisi; Cheng, Menyan

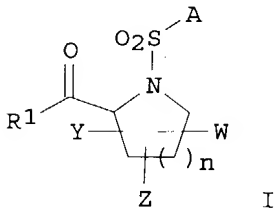
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 42 pp., Cont.-in-part of U.S. Ser. No. 888,675.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003105153	A1	20030605	US 2002-186531	20020701
US 6417219	B1	20020709	US 1997-918317	19970826
US 2002061877	A1	20020523	US 2001-888675	20010625
US 6569855	B2	20030527		
US 2002072517	A1	20020613	US 2001-888759	20010625
US 2003191163	A1	20031009	US 2002-308780	20021203
JP 2004115531	A2	20040415	JP 2003-384116	20031113
US 2004138260	A1	20040715	US 2003-730572	20031208

PRIORITY APPLN. INFO.:

US 1996-24842P	P	19960828
US 1997-918317	A2	19970826
US 2001-888675	A2	20010625
US 2001-888759	A2	20010625
JP 1998-511715	A3	19970822
US 2002-186531	A2	20020701

OTHER SOURCE(S): MARPAT 139:22213
GI



I

AB The invention provides compds. having a structure according to formula (I) [wherein A = each (un)substituted alkyl, heteroalkyl, aryl, heteroaryl; R1 = NHOR2 (where R2 = hydrogen or alkyl); W = H, lower alkyl, or an alkylene bridge that forms a ring in addition to the ring depicted in the formula; Y = HO, SR3, SOR4, SO2R8, alkoxy, (un)substituted NH2; R4 = alkyl, aryl, heteroaryl; R8 = alkyl, aryl, heteroaryl, heteroalkyl, amino, alkylamino, dialkylamino, arylamino, diarylamino, alkylarylamino; Z = H, HO, alkyl, or an alkylene or heteroalkylene bridge that forms a ring in addition to the ring depicted in the formula; n = 1; provisos given] or pharmaceutically acceptable salts, or biohydrolyzable amides, esters, or imides thereof. These compds. are useful as inhibitors of **metalloproteases**, in particular zinc **metalloprotease**, and effective in treating conditions characterized by excess activity of these enzymes, e.g. degenerative diseases such as arthritis and multiple sclerosis and inflammation (no data). Thus, cis-Hydroxy-D-proline (50 g, 0.38 mol) was dissolved in water:dioxane (1:1, 300 mL) with Et3N (135 mL, 0.96 mol), treated with 4-Methoxyphenylsulfonyl chloride (87 g, 0.42 mol) along with 2,6-dimethylaminopyridine (4.6 g, 0.038 mol), stirred for 14 h at room temperature, concentrated, and diluted with EtOAc to give, after workup, N-(4-Methoxyphenylsulfonyl)-(4R)-hydroxypyrrolidine-(2R)-carboxylic acid.

This intermediate was dissolved in MeOH (500 mL), treated dropwise with 50 mL SOCl2, stirred for 14 h, evaporated, to dryness, and triturated with CHCl3 to give N-4-Methoxyphenylsulfonyl-(2R)-carbomethoxy-(4R)-hydroxypyrrolidine as a white solid which was sufficiently pure to carry forward without purification The latter Me ester (361 mg, 1.15 mmol) was taken in 1 mL MeOH, treated with NH2OK (1.45 mL, 0.86 M in methanol), and stirred overnight to give, after workup, N-4-Methoxyphenylsulfonyl-(2R)-N-hydroxycarboxamido-(4S)-hydroxypyrrolidine.

ED Entered STN: 06 Jun 2003

IC ICM A61K031-4025
ICS A61K031-401

NCL 514422000; 514423000

CC 28-9 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1, 7, 27

ST cyclic amine prepn **metalloprotease** inhibitor; hydroxycarboxamidohydroxypyrrolidine prepn **metalloprotease** inhibitor; hydroxypyrrolidine hydroxycarboxamido prepn **metalloprotease** inhibitor; degenerative disease arthritis multiple sclerosis treatment pyrrolidine prepn; inflammation treatment pyrrolidine prepn

IT Amines, preparation
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(cyclic; preparation of substituted cyclic amines as **metalloprotease** inhibitors for treating conditions characterized by excess activity of these enzymes)

IT Disease, animal
(degenerative; preparation of substituted cyclic amines as **metalloprotease** inhibitors for treating conditions characterized by excess activity of these enzymes)

IT Anti-inflammatory agents
Antiarthritics
Arthritis
Inflammation
Multiple sclerosis
(preparation of substituted cyclic amines as **metalloprotease** inhibitors for treating conditions characterized by excess activity of these enzymes)

IT 204071-71-6P, N-[4-(2-Methoxyethoxy)phenylsulfonyl]-(2R)-(N-hydroxycarboxamido)-(4R)-hydroxypyrrolidine 204072-54-8P, N-[4-(2-Methoxyethoxy)phenylsulfonyl]-(2R)-methoxycarbonyl-(4R)-hydroxypyrrolidine
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(intermediate; preparation of substituted cyclic amines as **metalloprotease** inhibitors for treating conditions characterized by excess activity of these enzymes)

IT 1138-54-1P, 4-(Isobutoxy)phenylsulfonyl chloride 57850-07-4P, N-(4-Methylphenylsulfonyl)-(2R)-methoxycarbonyl-(4R)-hydroxypyrrolidine 203934-42-3P, N-(4-Methoxyphenylsulfonyl)-(2R)-methoxycarbonyl-4-oxopyrrolidine 203934-63-8P 203934-71-8P 203994-66-5P, N-(4-Methoxyphenylsulfonyl)-(2R)-carboxy-(4R)-hydroxypyrrolidine 203994-80-3P, N-(4-Methoxyphenylsulfonyl)-(2R)-methoxycarbonyl-(4R)-hydroxypyrrolidine 203994-82-5P, N-(4-Methoxyphenylsulfonyl)-(2R)-methoxycarbonyl-(4S)-**acetylthiopyrrolidine** 204072-15-1P, N-(4-Methoxyphenylsulfonyl)-(2R)-methoxycarbonyl-(4S)-benzoyloxypyrrolidine 204072-16-2P, N-(4-Methoxyphenylsulfonyl)-(2S)-methoxycarbonyl-(4R)-hydroxypyrrolidine 204072-17-3P,

N-(4-Methoxyphenylsulfonyl)-(2S)-methoxycarbonyl-(4S)-hydroxypyrrolidine 204072-18-4P, N-(4-Methoxyphenylsulfonyl)-(2R)-carboxy-(4S)-hydroxypyrrolidine 204072-19-5P, N-(4-Methoxyphenylsulfonyl)-(2R)-methoxycarbonyl-(4S)-methoxypyrrolidine 204072-20-8P, N-(4-Methoxyphenylsulfonyl)-(2R)-methoxycarbonyl-(4R)-(trifluoromethanesulfonyloxy)pyrrolidine 204072-21-9P 204072-23-1P, N-(4-Methoxyphenylsulfonyl)-(2R)-methoxycarbonyl-(4R)-[(benzothiazol-2-yl)**thio**]pyrrolidine 204072-24-2P, N-(4-Methoxyphenylsulfonyl)-(2R)-methoxycarbonyl-(4S)-[N-methyl-2-**imidazolylthio**]pyrrolidine 204072-25-3P, N-(4-Methoxyphenylsulfonyl)-(2R)-methoxycarbonyl-(4R)-[N-methyl-2-**imidazolylthio**]pyrrolidine 204072-26-4P, N-(4-Methoxyphenylsulfonyl)-(2R)-methoxycarbonyl-(4S)-phenoxypyrrolidine 204072-27-5P, N-(4-Methoxyphenylsulfonyl)-(2R)-methoxycarbonyl-(4S)-(4-benzyloxyphenoxy)pyrrolidine 204072-28-6P, N-(4-Methoxyphenylsulfonyl)-(2R)-methoxycarbonyl-(4S)-(3-phenylaminophenoxy)pyrrolidine 204072-29-7P, N-(4-Methoxyphenylsulfonyl)-(2R)-methoxycarbonyl-(4S)-(3-pyridinyloxy)pyrrolidine 204072-30-0P, N-(4-Methoxyphenylsulfonyl)-(2R)-methoxycarbonyl-(4S)-**phenylthiopyrrolidine** 204072-31-1P, N-(4-Methoxyphenylsulfonyl)-(2R)-methoxycarbonyl-(4R)-(methanesulfonyloxy)pyrrolidine 204072-32-2P, N-(4-Methoxyphenylsulfonyl)-(2R)-methoxycarbonyl-(4S)-(4-**methoxyphenylthio**)pyrrolidine 204072-34-4P, N-(4-Methoxyphenylsulfonyl)-(2R)-methoxycarbonyl-(4S)-(3-**methoxyphenylthio**)pyrrolidine 204072-36-6P, N-(4-Methoxyphenylsulfonyl)-(2R)-methoxycarbonyl-(4R)-ethoxymethoxypyrrolidine 204072-37-7P, N-(4-Methoxyphenylsulfonyl)-(2R)-methoxycarbonyl-(4R)-benzyloxymethoxypyrrolidine 204072-38-8P, N-(4-Methoxyphenylsulfonyl)-(2R)-methoxycarbonyl-(4R)-[(2-methoxyethoxy)methoxy]pyrrolidine 204072-39-9P 204072-40-2P, N-(4-Methoxyphenylsulfonyl)-(2R)-carboxy-4-oxopyrrolidine 204072-41-3P, N-(4-Methoxyphenylsulfonyl)-(2R)-methoxycarbonyl-(4R)-4-hydroxy-4-ethylpyrrolidine 204072-42-4P, N-(4-Methoxyphenylsulfonyl)-(2R)-methoxycarbonyl-(4R)-4-hydroxy-4-phenylpyrrolidine 204072-44-6P, N-(4-Methoxyphenylsulfonyl)-(2R)-methoxycarbonyl-3,3-dimethyl-4-oxopyrrolidine 204072-45-7P, N-(4-Methoxyphenylsulfonyl)-(2R)-methoxycarbonyl-3,3-dimethyl-(4R)-hydroxypyrrolidine 204072-46-8P, N-(3,4-Dimethoxyphenylsulfonyl)-(2R)-methoxycarbonyl-(4R)-hydroxypyrrolidine 204072-47-9P, N-(2-Nitro-4-methoxyphenylsulfonyl)-(2R)-methoxycarbonyl-(4R)-hydroxypyrrolidine 204072-49-1P, N-(4-Butoxyphenylsulfonyl)-(2R)-methoxycarbonyl-(4S)-benzoyloxypyrrolidine 204072-50-4P, N-(4-Bromobenzenesulfonyl)-(2R)-methoxycarbonyl-(4R)-hydroxypyrrolidine 204072-51-5P, N-(2-Methyl-4-bromobenzenesulfonyl)-(2R)-methoxycarbonyl-(4R)-hydroxypyrrolidine 204072-52-6P, N-(2,4-Dichlorophenylsulfonyl)-(2R)-methoxycarbonyl-(4R)-hydroxypyrrolidine 204072-53-7P, 4-(2-Methoxyethoxy)phenylsulfonyl chloride 204072-55-9P, N-(4-Phenoxyphenylsulfonyl)-(2R)-methoxycarbonyl-(4R)-hydroxypyrrolidine 204072-56-0P, N-(4-Isobutyloxyphenylsulfonyl)-(2R)-methoxycarbonyl-(4R)-hydroxypyrrolidine 204072-57-1P, N-(2-Methyl-4-bromophenylsulfonyl)-(2R)-methoxycarbonyl-(4S)-(3-**methoxyphenylthio**)pyrrolidine 204072-58-2P, N-(4-Butoxyphenylsulfonyl)-(2R)-methoxycarbonyl-(4S)-(2-**benzothiazolylthio**)pyrrolidine 204072-59-3P, N-(2-Nitro-4-Methoxyphenylsulfonyl)-(2R)-methoxycarbonyl-(4S)-(2-**benzothiazolylthio**)pyrrolidine 204072-60-6P, N-(4-Butoxyphenylsulfonyl)-(2R)-Methoxycarbonyl-(4S)-(4-**methoxyphenylthio**)pyrrolidine 204072-61-7P, N-(4-Butoxyphenylsulfonyl)-(2R)-methoxycarbonyl-(4S)-(3-pyridyloxy)pyrrolidine 204072-62-8P, N-(4-Methoxyphenylsulfonyl)-(2R)-methoxycarbonyl-(4S)-azidopyrrolidine 204072-64-0P, N-(4-Butoxyphenylsulfonyl)-(2R)-methoxycarbonyl-(4R)-(methylsulfonoxy)pyrrolidine 204072-65-1P, N-(4-Butoxyphenylsulfonyl)-(2R)-methoxycarbonyl-(4S)-azidopyrrolidine

204072-66-2P, N-(4-Butoxyphenylsulfonyl)-(2R)-methoxycarbonyl-(4S)-aminopyrrolidine 204072-67-3P, N-(4-Methoxyphenylsulfonyl)-(2R)-methoxycarbonyl-(4S)-propylaminopyrrolidine 204072-68-4P, N-(4-Methoxyphenylsulfonyl)-(2R)-methoxycarbonyl-(4S)-n-hexylaminopyrrolidine 204072-69-5P, N-(4-Methoxyphenylsulfonyl)-(2R)-methoxycarbonyl-(4S)-(2-phenylethylamino)pyrrolidine 204072-70-8P, N-(4-Methoxyphenylsulfonyl)-(2R)-methoxycarbonyl-(4S)-(N-butyl-N-hexylamino)pyrrolidine 204072-71-9P 204072-72-0P, N-(4-Butoxyphenylsulfonyl)-(2R)-methoxycarbonyl-(4S)-[(methanesulfonyl)amino]pyrrolidine 204072-74-2P, N-(4-Methoxyphenylsulfonyl)-(2R)-methoxycarbonyl-(4S)-[(3-pyridylmethyl)amino]pyrrolidine 204072-75-3P, N-(4-Methoxyphenylsulfonyl)-(2R)-methoxycarbonyl-(4S)-[N-(3-pyridylmethyl)-N-(methanesulfonyl)amino]pyrrolidine 204072-76-4P, N-(4-Methoxyphenylsulfonyl)-(2R)-methoxycarbonyl-(4S)-[N,N-bis(methanesulfonyl)amino]pyrrolidine 204072-77-5P, N-(4-Methoxyphenylsulfonyl)-(2R)-methoxycarbonyl-(4S)-[N-(methanesulfonyl)propylamino]pyrrolidine 204072-78-6P, N-(4-Methoxyphenylsulfonyl)-(2R)-methoxycarbonyl-(4S)-[(4-methoxyphenylsulfonyl)amino]pyrrolidine 204072-79-7P, N-(4-Methoxyphenylsulfonyl)-(2R)-methoxycarbonyl-(4S)-(1-oxohexyl)aminopyrrolidine 204072-81-1P 204072-82-2P, N-(4-Methoxyphenylsulfonyl)-(2R)-methoxycarbonyl-(4S)-[((2R)-1-oxo-2-benzyloxypropyl)amino]pyrrolidine 204072-83-3P, N-(4-Methoxyphenylsulfonyl)-(2R)-methoxycarbonyl-(4S)-[[(2R)-1-oxo-2-benzyloxy-3-phenylpropyl]amino]pyrrolidine 204072-84-4P, N-(4-Methoxyphenylsulfonyl)-(2R)-methoxycarbonyl-(4S)-[N-[(2R)-1-oxo-2-benzyloxypropyl]propylamino]pyrrolidine 204072-85-5P, N-(4-Methoxyphenylsulfonyl)-(2R)-methoxycarbonyl-(4S)-[N-[(2R)-1-oxo-2-hydroxypropyl]propylamino]pyrrolidine 204072-86-6P, N-(4-Methoxyphenylsulfonyl)-(2R)-methoxycarbonyl-(4S)-[N-((2R)-1-oxo-2-benzyloxy-3-phenylpropyl)propylamino]pyrrolidine 204072-87-7P, N-(4-Methoxyphenylsulfonyl)-(2R)-methoxycarbonyl-(4S)-[N-((2R)-1-oxo-2-hydroxy-3-phenylpropyl)propylamino]pyrrolidine 204072-88-8P, N-(4-Methoxyphenylsulfonyl)-(2R)-methoxycarbonyl-(4S)-(1-piperidyl)pyrrolidine 204072-89-9P, N-(4-Butoxyphenylsulfonyl)-(2R)-methoxycarbonyl-(4S)-(1-piperidyl)pyrrolidine 204072-90-2P, N-(4-Methoxyphenylsulfonyl)-(2R)-methoxycarbonyl-(4S)-morpholinopyrrolidine 204072-91-3P, N-(4-Butoxyphenylsulfonyl)-(2R)-methoxycarbonyl-(4S)-morpholinopyrrolidine 204072-92-4P, N-(4-Methoxyphenylsulfonyl)-(2R)-methoxycarbonyl-(4S)-(1,1-**dioxothiomorpholino**)pyrrolidine 204072-93-5P, N-(4-Butoxyphenylsulfonyl)-(2R)-methoxycarbonyl-(4S)-(1,1-**dioxothiomorpholino**)pyrrolidine 204073-01-8P 204073-02-9P 537704-28-2P 537704-31-7P, N-(4-Methoxyphenylsulfonyl)-(2R)-methoxycarbonyl-(4S)-aminopyrrolidine formate 537704-32-8P, N-(4-Butoxyphenylsulfonyl)-(2R)-methoxycarbonyl-(4S)-[[(N-methyl-3-imidazolyl)sulfonyl]amino]pyrrolidine 537704-35-1P 537704-63-5P, N-(4-Methoxyphenylsulfonyl)-(2R)-methoxycarbonyl-(4S)-(2,5-dioxo-1-methylimidazolidin-3-yl)pyrrolidine 537704-66-8P, N-(4-Butoxyphenylsulfonyl)-(2R)-methoxycarbonyl-(4S)-(2,5-dioxo-1-methylimidazolidin-3-yl)pyrrolidine 537704-68-0P, N-(4-Butoxyphenylsulfonyl)-(2R)-methoxycarbonyl-(4S)-(1-allyl-2,5-dioxoimidazolidin-3-yl)pyrrolidine 537704-72-6P, N-(4-Butoxyphenylsulfonyl)-(2R)-methoxycarbonyl-(4S)-(2,4-dioxo-5,5-dimethylimidazolidin-1-yl)pyrrolidine 537704-74-8P, N-(4-Butoxyphenylsulfonyl)-(2R)-methoxycarbonyl-(4S)-[(5S)-5-methyl-2,4-dioxoimidazolidin-1-yl]pyrrolidine 537704-76-0P, N-[4-(2-Methoxyethoxy)phenylsulfonyl]-(2R)-methoxycarbonyl-(4S)-(3-methyl-2,4-dioxoimidazolidin-1-yl)pyrrolidine 537704-78-2P, N-(4-

Phenoxyphenylsulfonyl)-(2R)-methoxycarbonyl-(4S)-(3-methyl-2,4-dioxoimidazolidin-1-yl)pyrrolidine
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; preparation of substituted cyclic amines as **metalloprotease** inhibitors for treating conditions characterized by excess activity of these enzymes)

IT 81669-70-7, **Metalloprotease**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(preparation of substituted cyclic amines as **metalloprotease** inhibitors for treating conditions characterized by excess activity of these enzymes)

IT 203934-18-3P 204071-36-3P, N-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-hydroxypyrrolidine 204071-38-5P, N-(4-Methoxyphenylsulfonyl)-(2S)-(N-hydroxycarboxamido)-(4R)-hydroxypyrrolidine 204071-40-9P, N-(4-Methoxyphenylsulfonyl)-(2S)-(N-hydroxycarboxamido)-(4S)-hydroxypyrrolidine 204071-42-1P, N-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-methoxypyrrolidine 204071-43-2P, N-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-[(benzothiazol-2-yl)**thio**]pyrrolidine 204071-44-3P, N-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4R)-[(benzothiazol-2-yl)**thio**]pyrrolidine 204071-45-4P, N-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-[N-methyl-2-**imidazolylthio**]pyrrolidine 204071-46-5P, N-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4R)-[N-methyl-2-**imidazolylthio**]pyrrolidine 204071-47-6P, N-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-phenoxypyrrolidine 204071-48-7P, N-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-(4-benzyloxyphenoxy)pyrrolidine 204071-49-8P, N-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-(3-phenylaminophenoxy)pyrrolidine 204071-50-1P, N-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-(3-pyridinyloxy)pyrrolidine 204071-51-2P, N-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-**phenylthiopyrrolidine** 204071-52-3P, N-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-(4-**methoxyphenylthio**)pyrrolidine 204071-53-4P, N-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-(3-**methoxyphenylthio**)pyrrolidine 204071-54-5P, N-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4R)-ethoxymethoxypyrrolidine 204071-55-6P, N-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4R)-benzyloxymethoxypyrrolidine 204071-56-7P, N-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4R)-[(2-methoxyethoxy)methoxy]pyrrolidine 204071-57-8P, N-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-**mercaptopyrrolidine** 204071-58-9P 204071-59-0P, N-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4R)-4-hydroxy-4-ethylpyrrolidine 204071-60-3P, N-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4R)-4-hydroxy-4-phenylpyrrolidine 204071-62-5P, N-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-3,3-dimethyl-(4R)-hydroxypyrrolidine 204071-63-6P, N-(4-Methylphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-hydroxypyrrolidine 204071-64-7P, N-(3,4-Dimethoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4R)-hydroxypyrrolidine 204071-65-8P, N-(2-Nitro-4-methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4R)-hydroxypyrrolidine 204071-66-9P, N-(4-Butoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4R)-hydroxypyrrolidine 204071-67-0P, N-(4-Butoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-hydroxypyrrolidine 204071-68-1P, N-(4-Bromobenzenesulfonyl)-(2R)-(N-hydroxycarboxamido)-(4R)-hydroxypyrrolidine 204071-69-2P, N-(2-Methyl-4-bromobenzenesulfonyl)-(2R)-(N-hydroxycarboxamido)-(4R)-hydroxypyrrolidine 204071-70-5P,

N-(2,4-Dichlorophenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4R)-hydroxypyrrolidine 204071-72-7P, N-(4-Phenoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4R)-hydroxypyrrolidine 204071-73-8P, N-(4-Isobutyloxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4R)-hydroxypyrrolidine 204071-74-9P, N-(2-Methyl-4-bromophenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-(3-**methoxyphenylthio**)pyrrolidine 204071-75-0P, N-(4-Butoxyphenylsulfonyl)-(2R)-(N-Hydroxycarboxamido)-(4S)-(2-**benzothiazolylthio**)pyrrolidine 204071-76-1P, N-(2-Nitro-4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-(2-**benzothiazolylthio**)pyrrolidine 204071-77-2P, N-(4-Butoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-(4-**methoxyphenylthio**)pyrrolidine 204071-78-3P, N-(4-Butoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-(3-pyridyloxy)pyrrolidine 204071-79-4P, N-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-aminopyrrolidine 204071-80-7P, N-(4-Butoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-aminopyrrolidine 204071-81-8P, N-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-propylaminopyrrolidine 204071-82-9P, N-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-n-hexylaminopyrrolidine 204071-83-0P, N-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-(2-phenylethylamino)pyrrolidine 204071-84-1P, N-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-(N-butyl-N-hexylamino)pyrrolidine 204071-85-2P, N-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-[(methanesulfonyl)amino]pyrrolidine 204071-86-3P, N-(4-Butoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-[(methanesulfonyl)amino]pyrrolidine 204071-88-5P, N-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-[N-(3-pyridylmethyl)-N-(methanesulfonyl)amino]pyrrolidine 204071-89-6P, N-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-[N,N-bis(methanesulfonyl)amino]pyrrolidine 204071-90-9P, N-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-[N-(methanesulfonyl)propylamino]pyrrolidine 204071-91-0P, N-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-[(4-methoxyphenylsulfonyl)amino]pyrrolidine 204071-92-1P, N-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-(1-oxohexylamino)pyrrolidine 204071-94-3P 204071-95-4P, N-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-[((2R)-1-oxo-2-benzyloxypropyl)amino]pyrrolidine 204071-96-5P, N-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-[[(2R)-1-oxo-2-benzyloxy-3-phenylpropyl]amino]pyrrolidine 204071-98-7P, N-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-[N-((2R)-1-oxo-2-hydroxy-3-phenylpropyl)propylamino]pyrrolidine 204071-99-8P, N-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-(1-piperidyl)pyrrolidine 204072-00-4P, N-(4-Butoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-(1-piperidyl)pyrrolidine 204072-01-5P, N-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-morpholinopyrrolidine 204072-02-6P, N-(4-Butoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-morpholinopyrrolidine 204072-03-7P, N-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-(1,1-**dioxothiomorpholino**)pyrrolidine 204072-04-8P, N-(4-Butoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-(1,1-**dioxothiomorpholino**)pyrrolidine 204072-12-8P 537704-26-0P, N-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4R)-hydroxypyrrolidine 537704-29-3P 537704-34-0P, N-(4-Butoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-[[(N-methyl-3-imidazolyl)sulfonyl]amino]pyrrolidine 537704-36-2P 537704-43-1P, N-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-[N-[(2R)-1-oxo-2-hydroxypropyl]propylamino]pyrrolidine 537704-65-7P, N-(4-Methoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-(2,5-dioxo-1-methylimidazolidin-3-yl)pyrrolidine 537704-67-9P, N-(4-

Butoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-(2,5-dioxo-1-methylimidazolidin-3-yl)pyrrolidine 537704-69-1P, N-(4-Butoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-(2,5-dioxo-1-allylimidazolidin-3-yl)pyrrolidine 537704-73-7P, N-(4-Butoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-(2,4-dioxo-5,5-dimethylimidazolidin-1-yl)pyrrolidine 537704-75-9P, N-(4-Butoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-[(5S)-5-methyl-2,4-dioxoimidazolidin-1-yl]pyrrolidine 537704-77-1P, N-[4-(2-Methoxyethoxy)phenylsulfonyl]-(2R)-(N-hydroxycarboxamido)-(4S)-(3-methyl-2,4-dioxoimidazolidin-1-yl)pyrrolidine 537704-79-3P, N-(4-Phenoxyphenylsulfonyl)-(2R)-(N-hydroxycarboxamido)-(4S)-(3-methyl-2,4-dioxoimidazolidin-1-yl)pyrrolidine 537704-80-6P, N-(4-Methoxyphenylsulfonyl)-(2R)-hydroxycarboxamido-(4R)-4-hydroxy-4-ethylpyrrolidine 538350-55-9P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of substituted cyclic amines as **metalloprotease** inhibitors for treating conditions characterized by excess activity of these enzymes)

IT 3970-21-6, 2-Methoxyethoxymethyl chloride
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of substituted cyclic amines as **metalloprotease** inhibitors for treating conditions characterized by excess activity of these enzymes)

IT 204073-03-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of substituted cyclic amines as **metalloprotease** inhibitors for treating conditions characterized by excess activity of these enzymes)

IT 60-56-0, 2-**Mercapto**-1-methylimidazole 65-85-0, Benzoic acid, reactions 74-88-4, Methyl iodide, reactions 75-08-1, **Ethanethiol** 77-71-4, 5,5-Dimethylhydantoin 98-58-8, 4-Bromobenzenesulfonyl chloride 98-59-9, p-Toluenesulfonyl chloride 98-68-0, 4-Methoxyphenylsulfonyl chloride 100-39-0, Benzyl bromide 100-46-9, Benzylamine, reactions 100-58-3, Phenylmagnesium bromide 101-18-8, 3-Hydroxydiphenylamine 103-16-2, 4-(Benzyloxy)phenol 108-98-5, **Thiophenol**, reactions 109-00-2, 3-Hydroxypyridine 111-26-2, Hexylamine 111-30-8, Glutaric dialdehyde 122-78-1, Phenylacetaldehyde 123-38-6, Propionaldehyde, reactions 124-63-0, Methanesulfonyl chloride 140-66-9, 4-Octylphenol 142-61-0, Hexanoyl chloride 149-30-4, 2-**Mercaptobenzothiazole** 149-87-1 334-88-3, Diazomethane 358-23-6 500-22-1, 3-Pyridinecarboxaldehyde 507-09-5, **Thioacetic** acid, reactions 616-04-6, 1-Methylhydantoin 624-83-9, Methyl isocyanate 627-42-9 696-63-9, 4-**Methoxythiophenol** 925-90-6, Ethylmagnesium bromide 1138-56-3, p-Butoxyphenylsulfonyl chloride 1499-56-5, trans-4-Hydroxy-L-proline methyl ester 1623-92-3, 4-Phenoxyphenylsulfonyl chloride 2051-62-9, 1,1'-Biphenyl-4-yl chloride 2584-71-6, cis-4-Hydroxy-D-proline 3366-93-6, 1-Allylhydantoin 3587-60-8, Benzyl chloromethyl ether 5414-19-7, 2-Bromoethyl ether 6482-24-2, 2-Bromoethyl methyl ether 7326-19-4, D-3-Phenyllactic acid 7617-67-6, Bis(2-bromoethyl) sulfone 15570-12-4, 3-**Methoxythiophenol** 16271-33-3, 2,4-Dichlorobenzenesulfonyl chloride 18092-54-1 23095-31-0, 3,4-Dimethoxyphenylsulfonyl chloride 40856-73-3 51212-37-4 54571-66-3 81102-38-7, cis-4-Hydroxy-L-proline methyl ester 100836-85-9 114676-47-0 139937-37-4, 2-Methyl-4-bromobenzenesulfonyl chloride 182937-63-9, (2R)-2-Benzyloxy-3-phenylpropanoic acid 537704-27-1 537704-33-9

RL: RCT (Reactant); RACT (Reactant or reagent)
(reactant; preparation of substituted cyclic amines as **metalloprotease** inhibitors for treating conditions characterized by excess activity of these enzymes)

L21 ANSWER 9 OF 28 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:154246 HCAPLUS
DOCUMENT NUMBER: **138:187764**
TITLE: Preparation of 2-(azacyclylcarbonylamino)thiazoles as tyrosine kinase inhibitors
INVENTOR(S): Hartman, George D.; Tucker, Thomas J.; Sisko, John T.; Smith, Anthony M.; Lumma, William C., Jr.
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 101 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003015778	A1	20030227	WO 2002-US27156	20020813
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004192926	A1	20040930	US 2004-486574	20040211
PRIORITY APPLN. INFO.:			US 2001-313234P	P 20010817
			WO 2002-US27156	W 20020813

OTHER SOURCE(S): MARPAT 138:187764
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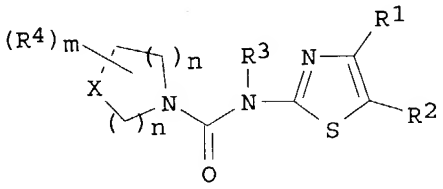

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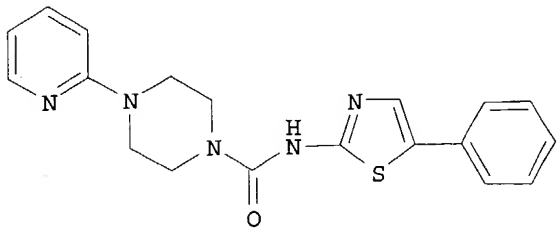

II

AB Title ureas I [wherein X = CH or NR3a; m = 1-6; n = independently 0-2; R1 = H, halo, alkyl, or alkoxy; R2 = (un)substituted aryl, CN, CONRaRb, halo, cycloalkyl, or C.tplbond.CRc; R3 = H, alkyl, SO2Rd, CORd, or CO2Rd; R3a = per the definition of R3 or substituted alkyl; R4 = H, alkylene-NR5R6, CO2H, CO2Rd, halo, OH, alkoxy, or (un)substituted alkyl; R5 and R6 = independently H, alkyl, SO2Rd, CO2Rd, CORd, alkylene-NRaRb, alkylene-CONRaRb, or (un)substituted alkylene-heterocyclyl or aryl; or NR5R6 = (un)substituted heterocyclyl; Ra and Rb = independently H, (cyclo)alkyl, Ph, CO2Rd, CORd, or SO2Rd; Rc = H, Ph, or alkyl; Rd = Ph or alkyl; or pharmaceutically acceptable salts or stereoisomers thereof] were prepared for the inhibition, regulation, and/or modulation tyrosine kinase signal transduction. For example, reaction of 2-[(4-nitrophenoxycarbonyl)amino]-5-phenylthiazole with 4-(2-pyridyl)piperazine in the presence of DIEA in DMF at 60° for 1 h gave II. Tested I inhibited VEGF-stimulated mitogenesis of human vascular endothelial cells in culture with IC50 values between 0.01 - 5.0 μM. I are useful for the treatment of tyrosine kinase-dependent diseases and conditions, such as angiogenesis, cancer, tumor growth, atherosclerosis, age related macular degeneration, diabetic retinopathy, inflammatory diseases, and the like in mammals (no data).

ED Entered STN: 28 Feb 2003

IC ICM A61K031-427
ICS A61K031-4439; A61K031-506; A61K031-5377; C07D417-12; C07D417-14

CC 28-7 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1

IT 9028-35-7, HMG-CoA reductase 9068-38-6, Reverse transcriptase 39391-18-9, Cyclooxygenase 131384-38-8, Prenyltransferase 141907-41-7, Matrix **metalloprotease** 144114-21-6, HIV protease 329900-75-6, COX 2
RL: BSU (Biological study, unclassified); BIOL (Biological study) (inhibitor, combination therapy agent; preparation of (azacyclylcarbonylamino)thiazole tyrosine kinase inhibitors as angiogenesis inhibitors)

RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Pharmacia & Upjohn S P	2000			WO 0026203 A1	HCAPLUS

L21 ANSWER 10 OF 28 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:905716 HCAPLUS
DOCUMENT NUMBER: **138:11438**
TITLE: Use of compounds with combined NEP/MP-inhibitory activity in the preparation of medicaments
INVENTOR(S): Berger, Claudia; Fischer, Yvan; Hoeltje, Dagmar; Waldeck, Harald; Weske, Michael; Ziegler, Dieter
PATENT ASSIGNEE(S): Solvay Pharmaceuticals Gmbh, Germany
SOURCE: PCT Int. Appl., 77 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002094176	A2	20021128	WO 2002-EP5259	20020514
WO 2002094176	A3	20031211		

W: AU, BR, CA, CN, CZ, DZ, HU, ID, IL, IN, JP, KR, MX, NO, NZ, PH,

PL, RU, SK, UA, US, ZA
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR

EP 1397141	A2	20040317	EP 2002-743004	20020514
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY, TR				
BR 2002009855	A	20040615	BR 2002-9855	20020514
US 2004162345	A1	20040819	US 2003-715112	20031118
PRIORITY APPLN. INFO.:			EP 2001-112231 A	20010518
			US 2001-292337P P	20010522
			WO 2002-EP5259 W	20020514

OTHER SOURCE(S): MARPAT 138:11438

AB This invention relates to the use of a compound having combined, in particular concurrent, inhibitors activity on neutral endopeptidase (NEP) and on a novel **metalloprotease** (MP) designated IGS5, or of a pharmaceutically acceptable salt or solvate or biolabile ester thereof, for the manufacture of a medicament (pharmaceutical composition) for treating a larger mammal, preferably a human, suffering from or being susceptible to a disease or condition which can be alleviated or prevented by combined or concurrent inhibition of NEP and IGS5. In a particular aspect the present invention pertains to the use of said compds. with combined or concurrent NEP/IGS5 inhibitory activity for treating a larger mammal, preferably a human, suffering from or being susceptible to a disease or condition where big-ET-1 levels are elevated and which disease or condition can be alleviated or prevented by combined or concurrent inhibition of NEP and IGS5. In a further particular aspect the present invention pertains to the use of said compds. with combined or concurrent NEP/IGS5 inhibitory activity for treating a larger mammal, preferably a human, suffering from or being susceptible to a disease or condition where ET-1 is significantly upregulated and which disease or condition can be alleviated or prevented by combined or concurrent inhibition of NEP and IGS5. In the present invention said compds. with combined or concurrent NEP/IGS5-inhibitory activity preferably are used for the treatment and/or prophylaxis of hypertension, including secondary forms of hypertension such as renal or pulmonary hypertension, heart failure, angina pectoris, arrhythmias, myocardial infarction, cardiac hypertrophy, cerebral ischemia, peripheral vascular disease, subarachnoidal hemorrhage, chronic obstructive pulmonary disease (COPD), asthma, renal disease, atherosclerosis, and pain in colorectal cancer or prostate cancer, in mammals, preferably in humans, and more preferably in a patient sub-population suffering from or being susceptible to a disease or condition which can be alleviated or prevented by combined or concurrent inhibition of NEP and IGS5. Furthermore, it may be beneficial to addnl. combine the said compds. showing combined or concurrent NEP/IGS5 inhibitory activity with other individual and/or combined **metalloprotease** inhibitors than the NEP/IGS5 inhibitors, e.g. with sep. ACE- and/or NEP-inhibitors and/or mixed inhibitors of these **metalloproteases.**

ED Entered STN: 29 Nov 2002

IC ICM A61K

CC 1-12 (Pharmacology)
Section cross-reference(s): 63

IT 36357-77-4, Phosphoramidon 76721-89-6, **Thiorphan**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(therapeutic use of compds. with combined NEP/MP-inhibitory activity)

L21 ANSWER 11 OF 28 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:540272 HCAPLUS
DOCUMENT NUMBER: **137:109216**
TITLE: Preparation of N-carboxymethylbenzolactams as matrix

metalloproteinase inhibitors

INVENTOR(S): Warshawsky, Alan M.; Janusz, Michael J.; Flynn, Gary A.

PATENT ASSIGNEE(S): USA

SOURCE: U.S. Pat. Appl. Publ., 41 pp., Cont. of U.S. Ser. No. 465,737, abandoned.
CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002095035	A1	20020718	US 2002-77913	20020220
US 6544980	B2	20030408		

PRIORITY APPLN. INFO.: US 1998-172244P P 19981231
US 1999-465737 B1 19991217

OTHER SOURCE(S): MARPAT 137:109216

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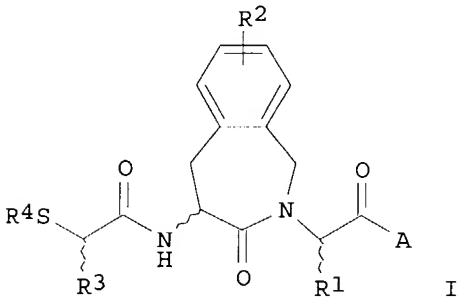


I

AB A method of inhibiting matrix metalloproteinases comprises administration of title compds. [I; A = OH, NRR'; R, R' = H, alkyl; NRR' = morpholino, piperidino, pyrrolidino, N-isoindolyl; R1 = alkyl, (CH2)4NH2, CH2OH, CH(OH)Me, etc.; R2 = H, halo, alkoxy, etc.; R3 = alkyl, (CH2)mW, (CH2)pAr, etc.; m = 2-8; p = 0-10; W = phthalimido; Ar = pyridyl, thienyl, quinolinyl, etc.; R4 = H, COR10, CO(CH2)qK, SG; R10 = H, alkyl, Ph, CH2Ph; q = 0-2; K = pyridyl, imidazolyl, etc.; G = pyridyl, (CH2)w(pyridyl), etc.; w = 1-3] (no data). Thus, tert-Bu 2-(4-amino-3-oxo-1,3,4,5-tetrahydrobenzo[c]azepin-2-yl)-4-methylvalerate, (S)-3-phenyl-2-**benzoylthiopropionic** acid, and EEDQ were stirred 18 h in CH2Cl2 to give 85% amide, which was stirred with CF3CO2H and anisole in CH2Cl2 to give 2-[4-(2-**benzoylthio**-2-phenylpropionylamino)-3-oxo-1,3,4,5-tetrahydrobenzo[c]azepin-2-yl]-4-methylvaleric acid.

ED Entered STN: 19 Jul 2002

IC ICM A61K031-55

NCL 540523000

CC 27-21 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 1, 34

IT 141907-41-7, Matrix **metalloprotease**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; preparation of N-carboxymethylbenzolactams as matrix metalloproteinase inhibitors)

L21 ANSWER 12 OF 28 HCAPLUS COPYRIGHT 2004 ACS on STN

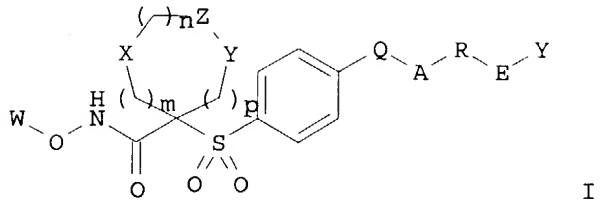
ACCESSION NUMBER: 2000:824220 HCAPLUS
DOCUMENT NUMBER: **134:17399**
TITLE: Aromatic sulfone hydroxamic acid **metalloprotease** inhibitors
INVENTOR(S): Barta, Thomas E.; Becker, Daniel P.; Bedell, Louis J.; Boehm, Terri L.; Carroll, Jeffrey N.; Decrescenzo, Gary A.; Fobian, Yvette M.; Freskos, John N.; Getman, Daniel P.; McDonald, Joseph J.; Hockerman, Susan L.; Howard, Susan C.; Kolodziej, Stephen A.; Li, Madeleine Hui; Mischke, Deborah A.; Rico, Joseph G.; Stehle, Nathan W.; Tollefson, Michael B.; Vernier, William F.; Villamil, Clara I.
PATENT ASSIGNEE(S): G.D. Searle and Co., USA
SOURCE: PCT Int. Appl., 616 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000069821	A1	20001123	WO 2000-US6719	20000515
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6750228	B1	20040615	US 2000-570731	20000512
CA 2372934	AA	20001123	CA 2000-2372934	20000515
EP 1183239	A1	20020306	EP 2000-930088	20000515
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
BR 2000010562	A	20030610	BR 2000-10562	20000515
JP 2003520196	T2	20030702	JP 2000-618238	20000515
AU 766792	B2	20031023	AU 2000-47970	20000515
NZ 515217	A	20040430	NZ 2000-515217	20000515
ZA 2001009006	A	20021202	ZA 2001-9006	20011031
NO 2001005543	A	20020110	NO 2001-5543	20011113

PRIORITY APPLN. INFO.:

US 1999-311837	A	19990514
US 2000-570731	A	20000512
US 1997-66007P	P	19971114
US 1998-95347P	P	19980804
US 1998-101080P	P	19980918
US 1999-256948	B2	19990224
WO 2000-US6719	W	20000515

OTHER SOURCE(S): MARPAT 134:17399
GI



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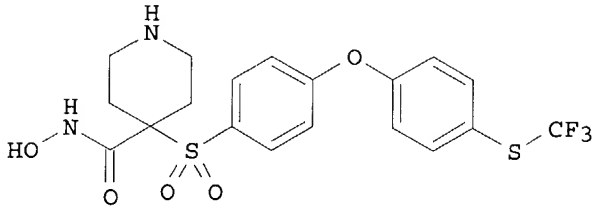

II

AB A treatment process is disclosed that comprises administering an effective amount of an aromatic sulfone hydroxamic acid I [W = H, cation, certain acyl or **thioacyl** groups; m, n, p = 0-2; (m+n+p) = 1 to 4; one of X, Y, and Z = CO, NH or derivs., O, S, SO, SO2, etc., and the other two = (un)substituted CH2; or XZ or ZY = (un)substituted NHCO, NHSO, NHSO2, SS, OCO, etc., and the other one = (un)substituted CH2; or n = 0 and XZY = atoms to complete various N/O/S heterocycles; Q = 5- to 7-membered heterocycle with 1-2 N atoms, one bound to Ph, and with -AREY bound in para-type positions; A = bond, O, S, (un)substituted NH, COO, OCO, CH:CH, C.tplbond.C, N:N, NHNH, NHCOO, (un)substituted CONH, NHCO, etc.; R = alkylene, arylene, heteroarylene, etc., with provisos; E = bond, CONH, NHCO, CO, SO2, NHSO2, SO2NH, S, etc.; Y = absent, H, alkyl, alkoxy, aryl, aryloxy, heteroaryl, etc.] to a host having a condition associated with pathol. matrix **metalloprotease** (**MMP**) activity. I exhibit excellent inhibitory activity of one or more **MMP** enzymes, such as **MMP**-2, **MMP**-9 and **MMP**-13, while exhibiting substantially less inhibition of (at least) **MMP**-1. Also disclosed are **metalloprotease** inhibitor compds. having such selective activities, processes for manufacture of such compds., and pharmaceutical compns. using such inhibitors. The compds. are potentially useful against a wide variety of conditions, notably as antiinflammatory, antiangiogenesis, and antitumor agents. Over 900 example compds. are listed, most with supporting phys. data, and many with synthetic details. For instance, Et N-(tert-butoxycarbonyl)-4-(4-fluorophenylsulfonyl)-4-piperidinecarboxylate (preparation given) was subjected to a sequence of: (1) etherification with 4-(CF3S)C6H4OH (100%); (2) alkaline hydrolysis of the ester (100%); (3) amidation with THP-ONH2 (45%); and (4) acid deprotection of the THP ether (40%), to give title compound II.HCl. The latter salt selectively inhibited **MMP**-13 with IC50 0.2 nM, and **MMP**-2 with IC50 0.1 nM, but with IC50 >10,000 nM against **MMP**-1.

ED Entered STN: 24 Nov 2000

IC ICM C07D211-66
ICS C07D405-12; C07D405-14; C07D309-08; C07D335-02; C07D409-12; C07D401-06; C07D401-12; A61K031-445; A61K031-4523; A61P009-00

CC 27-16 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 1, 7

ST arom sulfone hydroxamic acid prepn matrix **metalloprotease** inhibitor; **MMP** inhibitor prepn hydroxamic acid pyran

thiopyran piperidine

IT Angiogenesis inhibitors
Anti-inflammatory agents
Antitumor agents
(preparation of aromatic sulfone hydroxamic acids as **metalloprotease** inhibitors)

IT Hydroxamic acids
Sulfones
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of aromatic sulfone hydroxamic acids as **metalloprotease** inhibitors)

IT 9001-12-1, **MMP**-1 141907-41-7, Matrix **metalloprotease** 146480-35-5, **MMP** 2 146480-36-6, **MMP** 9 175449-82-8, **MMP**-13
RL: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)
(binding; preparation of aromatic sulfone hydroxamic acids as **metalloprotease** inhibitors)

IT 308822-81-3P 308822-82-4P 308822-86-8P 308822-95-9P 308823-05-4P 308824-05-7P 308824-24-0P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(drug candidate; preparation of aromatic sulfone hydroxamic acids as **metalloprotease** inhibitors)

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RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(drug candidate; preparation of aromatic sulfone hydroxamic acids as **metalloprotease** inhibitors)

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RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(drug candidate; preparation of aromatic sulfone hydroxamic acids as **metalloprotease** inhibitors)

IT 308826-90-6P 308826-92-8P 308826-93-9P 308826-94-0P 308826-95-1P
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308828-73-1P 308828-74-2P 308828-75-3P 308828-76-4P 308828-77-5P
308828-78-6P 308828-79-7P 308828-80-0P 308828-81-1P 308828-82-2P
308828-83-3P 308828-84-4P 308828-85-5P 308828-86-6P 308828-87-7P
308828-88-8P 308828-89-9P 308828-90-2P 308828-91-3P 308828-92-4P
308828-93-5P 308828-94-6P 308828-95-7P 308828-96-8P 308828-97-9P
308828-98-0P 308828-99-1P 308829-00-7P 308829-01-8P 308829-02-9P
308829-03-0P 308829-04-1P 308829-05-2P 308829-06-3P 308829-07-4P
308829-08-5P 308829-09-6P 308829-10-9P 308829-11-0P 308829-12-1P
308829-13-2P 308829-14-3P 308829-15-4P 308829-16-5P 308829-17-6P
308829-19-8P 308829-20-1P 308829-21-2P 308829-23-4P 308829-24-5P
308829-25-6P 308829-26-7P 308829-27-8P 308829-28-9P 308829-29-0P
308829-32-5P 308829-34-7P 308829-35-8P 308829-36-9P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological

study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(drug candidate; preparation of aromatic sulfone hydroxamic acids as **metalloprotease** inhibitors)

IT 308829-37-0P 308829-38-1P 308829-39-2P 308829-40-5P 308829-41-6P
308829-42-7P 308829-43-8P 308829-44-9P 308829-45-0P 308829-46-1P
308829-47-2P 308829-48-3P 308829-49-4P 308829-51-8P 308829-53-0P
308829-54-1P 308829-55-2P 308829-56-3P 308829-57-4P 308829-58-5P
308829-59-6P 308829-60-9P 308829-61-0P 308829-62-1P 308829-63-2P
308829-64-3P 308829-65-4P 308829-66-5P 308829-67-6P 308829-68-7P
308829-69-8P 308829-70-1P 308829-71-2P 308829-72-3P 308829-73-4P
308829-74-5P 308829-75-6P 308829-76-7P 308832-77-1P 308832-78-2P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(drug candidate; preparation of aromatic sulfone hydroxamic acids as **metalloprotease** inhibitors)

IT 405-31-2P 4783-86-2P 81151-35-1P 84358-13-4P 113113-66-9P
138647-49-1P 142851-03-4P 162881-76-7P 180695-79-8P 188527-08-4P
192329-80-9P 192330-49-7P 193022-95-6P 195503-42-5P 226388-52-9P
226388-56-3P 226388-60-9P 226389-21-5P 226389-49-7DP, resin-bound
226389-52-2P 226391-07-7DP, resin-bound 226395-65-9P 226395-75-1P
226395-93-3P 226396-02-7P 226396-03-8P 226396-33-4P 226396-34-5P
226396-40-3P 226396-42-5P 226396-44-7P 226396-51-6P 226396-53-8P
226396-54-9P 226396-56-1P 226396-62-9P 226396-63-0P 226396-64-1P
226396-65-2P 226396-66-3P 226396-67-4P 226396-70-9P 226396-71-0P
226396-72-1P 226397-96-2P 226398-02-3P 226398-13-6P 226399-44-6P
226399-45-7P 226399-47-9P 226399-49-1P 226399-50-4P 226399-52-6P
226399-90-2P 226399-91-3P 226399-92-4P 226399-95-7P 226400-29-9P
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226401-19-0P 226401-21-4P 226401-22-5P 226401-23-6P 226401-67-8P
226401-76-9P 287954-32-9P 308798-39-2P 308823-36-1DP, resin-bound
308823-46-3DP, resin-bound 308823-88-3P 308823-89-4P 308823-90-7P
308829-77-8DP, resin-bound 308829-78-9P 308829-79-0DP, resin-bound
308829-80-3DP, resin-bound 308829-81-4DP, resin-bound 308829-82-5P
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308830-95-7P 308830-96-8P 308830-97-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; preparation of aromatic sulfone hydroxamic acids as **metalloprotease** inhibitors)

IT 51-45-6, Histamine, reactions 62-53-3, Aniline, reactions 67-62-9, Methoxyamine 75-04-7, Ethylamine, reactions 78-81-9, Isobutylamine

90-04-0 95-51-2, 2-Chloroaniline 96-34-4, Methyl 2-chloroacetate
98-09-9, Benzenesulfonyl chloride 98-16-8, 3-(Trifluoromethyl)aniline
98-88-4, Benzoyl chloride 99-89-8, 4-Isopropylphenol 99-98-9,
N,N-Dimethyl-p-phenylenediamine 100-07-2, 4-Anisoyl chloride 100-39-0,
Benzyl bromide 100-46-9, Benzylamine, reactions 100-61-8,
N-Methylaniline, reactions 103-67-3, N-Benzylmethylamine 103-71-9,
Phenyl isocyanate, reactions 103-76-4, N-(2-Hydroxyethyl)piperazine
103-80-0, Phenylacetyl chloride 104-12-1, 4-Chlorophenyl isocyanate
104-81-4, 4-Methylbenzyl bromide 104-94-9 106-38-7, 4-Bromotoluene
106-96-7, Propargyl bromide 107-08-4, 1-Iodopropane 107-10-8,
1-Propylamine, reactions 108-00-9, N,N-Dimethylethylenediamine
108-42-9, 3-Chloroaniline 108-95-2, Phenol, reactions 108-98-5,
Thiophenol, reactions 109-00-2, 3-Hydroxypyridine 109-01-3,
1-Methylpiperazine 109-85-3, 2-Methoxyethylamine 109-89-7,
Diethylamine, reactions 109-90-0, Ethyl isocyanate 110-85-0,
Piperazine, reactions 110-89-4, Piperidine, reactions 110-91-8,
Morpholine, reactions 110-96-3, Diisobutylamine 111-49-9 111-95-5
122-04-3, 4-Nitrobenzoyl chloride 122-99-6, Ethylene glycol phenyl ether
123-75-1, Pyrrolidine, reactions 123-90-0, **Thiomorpholine**
124-02-7 124-40-3, Dimethylamine, reactions 141-43-5, Ethanolamine,
reactions 142-25-6, N,N,N'-Trimethylethylenediamine 150-76-5,
4-Methoxyphenol 156-87-6, 3-Amino-1-propanol 288-32-4, Imidazole,
reactions 288-88-0, 1H-1,2,4-Triazole 312-94-7, 2-
(Trifluoromethyl)benzoyl chloride 329-01-1, 3-(Trifluoromethyl)phenyl
isocyanate 329-15-7, 4-(Trifluoromethyl)benzoyl chloride 348-54-9,
2-Fluoroaniline 371-40-4, 4-Fluoroaniline 371-41-5, 4-Fluorophenol
371-42-6, 4-(Fluoro)**thiophenol** 372-19-0, 3-Fluoroaniline
393-52-2, 2-Fluorobenzoyl chloride 395-44-8, 2-(Trifluoromethyl)benzyl
bromide 402-23-3, 3-(Trifluoromethyl)benzyl bromide 402-45-9,
α,α,α-Trifluoro-p-cresol 403-43-0, 4-Fluorobenzoyl
chloride 404-71-7, 3-Fluorophenyl isocyanate 407-25-0, Trifluoroacetic
anhydride 421-83-0, Trifluoromethanesulfonyl chloride 455-14-1,
4-(Trifluoromethyl)aniline 459-46-1, 4-Fluorobenzyl bromide 461-82-5,
4-(Trifluoromethoxy)aniline 461-84-7, 4-(**Trifluoromethylthio**
)phenol 496-15-1, Indoline 498-94-2, Isonipecotic acid 504-24-5,
4-Aminopyridine 527-69-5, 2-Furoyl chloride 536-90-3 556-61-6,
Methyl **isothiocyanate** 591-54-8, 4-Aminopyrimidine 592-55-2,
2-Bromoethyl ethyl ether 616-45-5, 2-Pyrrolidinone 620-13-3,
3-Methylbenzyl bromide 622-95-7, 4-Chlorobenzyl bromide 625-43-4,
N-Methylisobutylamine 626-56-2, 3-Methylpiperidine 626-64-2,
4-Hydroxypyridine 627-37-2, N-Methylallylamine 658-46-8 694-05-3,
1,2,3,6-Tetrahydropyridine 753-90-2, 2,2,2-Trifluoroethylamine
777-44-6, 3-(Trifluoromethyl)benzenesulfonyl chloride 828-27-3,
p-(Trifluoromethoxy)phenol 874-60-2, 4-Toluoyl chloride 877-88-3,
3,5-Dimethoxybenzyl bromide 877-96-3, 1-[3-(Dimethylamino)propyl]piperaz
ine 929-06-6, 2-(2-Aminoethoxy)ethanol 933-88-0, 2-Toluoyl chloride
1008-91-9, 1-(4-Pyridyl)piperazine 1011-15-0, 1-(2-
Fluorophenyl)piperazine 1013-76-9, 1-(2,4-Dimethylphenyl)piperazine
1126-09-6, Ethyl isonipecotate 1195-45-5, 4-Fluorophenyl isocyanate
1423-27-4 1535-73-5, 3-(Trifluoromethoxy)aniline 1535-75-7,
2-(Trifluoromethoxy)aniline 1548-13-6, 4-(Trifluoromethyl)phenyl
isocyanate 1632-84-4, 4-(**Methylthio**)phenyl isocyanate
1645-65-4, 4-(Trifluoromethyl)phenyl **isothiocyanate** 1711-05-3,
3-Anisoyl chloride 1711-07-5, 3-Fluorobenzoyl chloride 1939-99-7,
α-Toluenesulfonyl chloride 2033-89-8, 3,4-Dimethoxyphenol
2038-57-5, Benzenepropanamine 2131-64-8, 4-(Dimethylamino)phenyl
isothiocyanate 2251-50-5, Pentafluorobenzoyl chloride
2251-65-2, 3-(Trifluoromethyl)benzoyl chloride 2252-63-3,
1-(4-Fluorophenyl)piperazine 2338-18-3 2516-47-4,
(Aminomethyl)cyclopropane 2836-04-6, N,N-Dimethyl-1,3-phenylenediamine

2971-79-1, Methyl isonipecotate 2991-42-6, 4-(Trifluoromethyl)benzenesulfonyl chloride 3173-56-6, Benzyl isocyanate 3202-33-3, 4-Phenoxypiperidine 3282-30-2, Pivaloyl chloride 3535-37-3, 3,4-Dimethoxybenzoyl chloride 3644-18-6, 1-[2-(Dimethylamino)ethyl]piperazine 3647-69-6, 4-(2-Chloroethyl)morpholine hydrochloride 3731-51-9, 2-(Aminomethyl)pyridine 3731-52-0, 3-(Aminomethyl)pyridine 3731-53-1, 4-(Aminomethyl)pyridine 4023-34-1, Cyclopropanecarbonyl chloride 4124-31-6, Trichloroacetic anhydride 4318-37-0, 1-Methylhomopiperazine 4318-42-7 4597-87-9, 2-(Methylamino)pyridine 4693-91-8, 4-Methoxyphenylacetyl chloride 4755-50-4, 4-(Dimethylamino)benzoyl chloride 4892-89-1, 1-(2-Morpholinoethyl)piperazine 5181-06-6, 1-(2-Methoxyphenyl)piperidine 5271-67-0, 2-**Thiophenecarbonyl** chloride 5292-43-3, tert-Butyl bromoacetate 5321-49-3, 1-(2-Phenylethyl)piperazine 5382-16-1, 4-Hydroxypiperidine 5414-19-7, Bis-(2-bromoethyl) ether 5638-76-6, 2-[2-(Methylamino)ethyl]pyridine 6269-89-2, 1-(4-Nitrophenyl)piperazine 6457-49-4, 4-(Hydroxymethyl)piperidine 6482-24-2, 2-Bromoethyl methyl ether 6485-55-8, cis-2,6-Dimethylmorpholine 6640-24-0, 1-(3-Chlorophenyl)piperazine 6711-48-4, 3,3'-Iminobis(N,N-dimethylpropylamine) 6723-30-4, O-(Tetrahydro-2H-pyran-2-yl)hydroxylamine 7357-67-7, 3-Morpholinopropyl chloride 7377-26-6, Methyl 4-(chlorocarbonyl)benzoate 7379-35-3, 4-Chloropyridine hydrochloride 10111-08-7, 2-Imidazolecarboxaldehyde 10400-19-8, Nicotinoyl chloride 13339-01-0, 1-(2-Ethoxyphenyl)piperazine 13349-82-1, 1-[2-(2-Hydroxyethoxy)ethyl]piperazine 13484-40-7, 1-(2-Methoxyethyl)piperazine 13889-98-0, 1-Acetylpiperazine 13961-36-9, 1-Allylpiperazine 14254-57-0, Isonicotinoyl chloride 14446-75-4, cis-3,5-Dimethylpiperidine 15268-31-2, 3-Pyridyl isocyanate 16413-26-6, 3-Cyanophenyl isocyanate 16744-98-2, 2-Fluorophenyl isocyanate 17201-43-3, 4-Cyanobenzyl bromide 17213-57-9, 3,5-Dimethoxybenzoyl chloride 17452-27-6 17739-45-6, 2-(2-Bromoethoxy)tetrahydro-2H-pyran 18880-04-1, 3,4-Dichlorobenzyl bromide 19853-09-9, 2-Phenylbenzyl bromide 20662-53-7 20980-22-7, 2-(1-Piperazinyl)pyrimidine 21043-40-3, 1-Cyclopentylpiperazine 21615-34-9, 2-Anisoyl chloride 21655-48-1, cis-2,6-Dimethylpiperazine 26389-60-6, N-Propylcyclopropanemethylamine 27129-86-8, 3,5-Dimethylbenzyl bromide 27374-25-0, [(1-Ethoxycyclopropyl)oxy]trimethylsilane 27757-85-3, 2-**Thiophenemethylamine** 30459-17-7, 1-[4-(Trifluoromethyl)phenyl]piperazine 32452-46-3, trans-3,5-Dimethylpiperidine 32459-62-4, 4-Ethoxyphenyl isocyanate 32813-24-4, 2-Piperidinoethyl **isothiocyanate** 33403-97-3, 4-(Ethylaminomethyl)pyridine 34803-66-2, 1-(2-Pyridyl)piperazine 34803-68-4, 1-(2-Pyrazinyl)piperazine 35161-71-8, N-Methylpropargylamine 35309-20-7, 3-Isocyanatopropionic acid 35386-24-4, 1-(2-Methoxyphenyl)piperazine 35730-09-7, 2,5-Difluorobenzoyl chloride 35794-11-7, 3,5-Dimethylpiperidine 35947-12-7, 1-(4-Methoxyphenyl)-2-methylpiperazine 36823-88-8, 4-(Trifluoromethoxy)benzoyl chloride 37517-81-0, Methyl malonyl chloride 38778-05-1, 4-(Phenoxy) **benzenethiol** 39512-50-0, 1-(2-Chlorophenyl)piperazine 39546-32-2, Isonipecotamide 39890-45-4, N-[2-(1-Piperazinyl)acetyl]pyrrolidine 40004-08-8, 1-(Ethoxycarbonylmethyl)piperazine 40172-95-0, 1-(2-Furoyl)piperazine 45597-00-0, cis-3,5-Dimethylmorpholine 49647-20-3, 4-Acetylphenyl isocyanate 50824-05-0, 4-(Trifluoromethoxy)benzyl bromide 51639-48-6 53460-46-1, 1,3,3-Trimethyl-6-azabicyclo[3.2.1]octane 54288-70-9, 4-Bromopiperidine hydrobromide 56346-57-7, 4-(4-Fluorobenzoyl)piperidine 56651-60-6, 4-Methoxybenzyl isocyanate 58315-38-1, N-[2-Nitro-4-(trifluoromethyl)phenyl]piperazine 58333-75-8, 4-(2-Methoxyphenyl)piperidine 63224-35-1, 2-Morpholinoethyl **isothiocyanate** 68337-15-5, 4-(1,2,4-Triazol-1-yl)phenol

68832-13-3 69628-75-7, 1-(1-Phenylethyl)piperazine 76362-12-4, 4-(4-Methoxybenzoyl)piperidine 76835-20-6, 1-(5-Chloro-2-methylphenyl)piperazine 79099-07-3 82911-69-1, N-(9-Fluorenylmethoxycarbonyloxy)succinimide 85118-01-0, 3,4-Difluorobenzyl bromide 85275-45-2 87394-63-6, 1-[3-(Trifluoromethyl)pyrid-2-yl]piperazine 103008-51-1, 2-(Trifluoromethoxy)benzenesulfonyl chloride 109384-19-2 115761-79-0, 1-(2,4-Difluorophenyl)piperazine 118708-88-6, 1-[4-(Trifluoromethyl)-2-pyridyl]piperazine 120104-92-9 132834-59-4, 1-[3-Chloro-5-(trifluoromethyl)pyrid-2-yl]piperazine 159689-88-0, 3-(Trifluoromethoxy)benzyl bromide 175277-80-2 179756-91-3, 1-[4-(Trifluoromethyl)-2-pyrimidyl]piperazine 226400-27-7 308830-98-0
RL: RCT (Reactant); RACT (Reactant or reagent)
(starting material; preparation of aromatic sulfone hydroxamic acids as **metalloprotease** inhibitors)

IT 308830-99-1 308831-00-7, 4-(3,5-Dimethylphenoxy)piperidine 308831-01-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(starting material; preparation of aromatic sulfone hydroxamic acids as **metalloprotease** inhibitors)

RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
American Cyanamid Co	1998			WO 9837877 A	HCAPLUS
American Cyanamid Co	1999			WO 9942436 A	HCAPLUS
Ciba Geigy Ag	1994			EP 0606046 A	HCAPLUS
Crescenzo Gary A de	1999			WO 9925687 A	HCAPLUS
Rhone Poulenc Rorer Pha	1997			WO 9724117 A	HCAPLUS

L21 ANSWER 13 OF 28 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:535102 HCAPLUS
DOCUMENT NUMBER: **133:150908**
TITLE: Preparation of acetylenic α-amino acid-based sulfonamide hydroxamic acid TACE inhibitors
INVENTOR(S): Levin, Jeremy Ian; Chen, James Ming; Cole, Derek Cecil
PATENT ASSIGNEE(S): American Cyanamid Company, USA
SOURCE: PCT Int. Appl., 293 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000044709	A2	20000803	WO 2000-US1981	20000127
WO 2000044709	A3	20001221		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2356299	AA	20000803	CA 2000-2356299	20000127
EP 1144368	A2	20011017	EP 2000-905750	20000127
EP 1144368	B1	20040714		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

BR 2000007752	A	20011204	BR 2000-7752		20000127
TR 200102132	T2	20020121	TR 2001-200102132		20000127
JP 2002535382	T2	20021022	JP 2000-595966		20000127
AU 766717	B2	20031023	AU 2000-27384		20000127
NZ 511928	A	20031128	NZ 2000-511928		20000127
AT 271035	E	20040715	AT 2000-905750		20000127
ZA 2001004326	A	20020826	ZA 2001-4326		20010525
NO 2001003674	A	20010924	NO 2001-3674		20010726
BG 105738	A	20020531	BG 2001-105738		20010726
PRIORITY APPLN. INFO.:			US 1999-238255	A	19990127
			WO 2000-US1981	W	20000127

OTHER SOURCE(S): MARPAT 133:150908

AB Amino acid derivs. HONHCOCR1R2NR3-X-Y-Z-CR4R5C.tplbond.CR6 [X = SO2, P(O)R10, where R10 = alkyl, cycloalkyl, aryl, heteroaryl; Y = aryl, heteroaryl, with the proviso that X and Z may not be bonded to adjacent atoms of Y; Z = O, NH, CH2, S; R1 = H, aryl, alkyl, alkenyl, alkynyl; R2 = any group given for R1, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, cycloheteroalkyl or R1 and R2 may form a ring; R3 = H, alkyl, cycloalkyl, cycloheteroalkyl, aralkyl, heteroaralkyl or R1 and R3 may form a ring; R4, R5 = H, alkyl, CN, C.tplbond.CH; R6 = any group given for R1, heteroaryl, cycloalkyl, cycloheteroalkyl] or pharmaceutically acceptable salts were prepared as inhibitors of TNF-α converting enzyme (TACE). Thus, 2-[(4-but-2-ynyloxybenzenesulfonyl)methylamino]-N-hydroxy-3-methylbutyramide was prepared and showed IC50 = 7.4 nM for inhibition of TACE.

ED Entered STN: 04 Aug 2000

IC ICM C07C311-00

CC 34-2 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1

IT 9001-12-1, **MMP**-1 146480-36-6, **MMP** 9 151769-16-3, Tace 175449-82-8, **MMP**-13
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(preparation of acetylenic α-amino acid-based sulfonamide hydroxamic acid TACE inhibitors)

IT 52-67-5, D-Penicillamine 55-22-1, Isonicotinic acid, reactions 59-67-6, Nicotinic acid, reactions 60-24-2, 2-**Mercaptoethanol** 62-57-7, 2-Aminoisobutyric acid 74-11-3 79-03-8, Propionyl chloride 88-10-8, Diethylcarbamoyl chloride 88-13-1, 3-**Thiophenecarboxylic** acid 98-68-0, 4-Methoxybenzenesulfonyl chloride 98-89-5, Cyclohexanecarboxylic acid 100-09-4, p-Anisic acid 103-71-9, Phenyl isocyanate, reactions 103-82-2, Phenylacetic acid, reactions 104-03-0, p-Nitrophenylacetic acid 104-94-9, p-Anisidine 106-54-7, 4-**Chlorobenzenethiol** 106-93-4, 1,2-Dibromoethane 106-96-7, Propargyl bromide 107-08-4, Propyl iodide 107-92-6, Butyric acid, reactions 108-95-2, Phenol, reactions 109-01-3, 1-Methylpiperazine 109-02-4, 4-Methylmorpholine 109-64-8, 1,3-Dibromopropane 109-70-6, 1-Bromo-3-chloropropane 110-65-6, 2-Butyne-1,4-diol 111-77-3, Di(ethylene glycol)mono methyl ether 112-35-6, Tri(ethylene glycol)mono methyl ether 112-80-1, Oleic acid, reactions 123-75-1, Pyrrolidine, reactions 137-00-8, 4-Methyl-5-thiazoleethanol 140-10-3, reactions 288-32-4, Imidazole, reactions 319-78-8, D-Isoleucine 349-88-2, 4-Fluorobenzenesulfonyl chloride 371-40-4 454-29-5, **Homocysteine** 501-52-0, Hydrocinnamic acid 507-19-7, 2-Bromo-2-methylpropane 513-38-2, 1-Iodo-2-Methylpropane 516-06-3, Valine 579-75-9, o-Anisic acid 586-76-5 589-15-1, p-Bromobenzyl bromide 617-27-6, DL-Alanine ethyl ester hydrochloride 623-33-6, Glycine ethyl ester hydrochloride 627-18-9, 1-Bromo-3-propanol 636-44-2, 2,5-Dimethyl-3-furoic acid 637-59-2, 1-Bromo-3-phenylpropane 764-01-2, 2-Butyn-1-ol 825-90-1,

4-Hydroxybenzenesulfonic acid sodium salt 921-01-7, D-**Cysteine** 928-90-5, 5-Hexyn-1-ol 1002-36-4, 2-Heptyn-1-ol 1192-63-8, 1-Pyrrolidinecarbonyl chloride 1445-73-4, 1-Methyl-4-piperidone 1504-58-1, 3-Phenyl-2-propyn-1-ol 2104-89-4, DL-Serine methyl ester 2510-36-3, 3,5-Dimethylisoxazole-4-carboxylic acid 2577-48-2, L-Proline methyl ester 2949-22-6, Ethyl isocyanatoacetate 2955-88-6, 1-(2-Hydroxyethyl)pyrrolidine 3031-68-3, 2,4-Hexadiyne-1,6-diol 3042-81-7, Methyl α-bromophenylacetate 3355-28-0, 1-Bromo-2-butyne 3445-11-2, 1-(2-Hydroxyethyl)-2-pyrrolidinone 3612-20-2, 1-Benzyl-4-piperidone 3647-69-6 4285-42-1, n-Methyl-n-phenylcarbamoyl chloride 4530-20-5 5271-67-0, 2-**Thiophenecarbonyl** chloride 5292-43-3, tert-Butyl bromoacetate 5350-93-6, 5-Amino-2-chloropyridine 5390-04-5, 4-Pentyn-1-ol 5619-05-6, DL-Valine methyl ester hydrochloride 5807-30-7, 3,4-Dichlorophenylacetic acid 6261-22-9, 2-Pentyn-1-ol 6480-68-8, 3-Quinolinecarboxylic acid 6940-78-9, 1-Bromo-4-chlorobutane 6959-48-4, 3-Picolyl chloride hydrochloride 7051-34-5, (Bromomethyl)cyclopropane 10465-81-3, 1,1'-(Azodicarbonyl)dipiperidine 14316-06-4, D-Alanine methyl ester hydrochloride 14328-64-4 15159-40-7, 4-Morpholinecarbonyl chloride 15260-83-0 15788-16-6, 5-Benzimidazolecarboxylic acid 16837-14-2 19009-39-3, Diisopropylcarbamoyl chloride 19225-92-4, 1-Methyl-2-chloromethylimidazole 19686-73-8, 1-Bromo-2-propanol 22818-40-2 24091-92-7 26690-80-2 26782-71-8, D-tert-Leucine 31608-23-8 34010-15-6, cis-11-Tetradecen-1-ol 34297-27-3, D-Penicillamine methyl ester hydrochloride 34893-92-0, 3,5-Dichlorophenyl isocyanate 37993-32-1 40365-61-5, 2-(3-Butynyloxy)tetrahydro-2h-pyran 41345-53-3, 2,4-Pentadiyn-1-ol 41994-51-8, 1,2,3,4-Tetrahydro-3-isoquinolinecarboxylic acid hydrochloride 52605-49-9, Sarcosine ethyl ester hydrochloride 57561-39-4 58885-58-8 59337-89-2, 3-**Chlorothiophene**-2-carboxylic acid 60421-23-0 68641-49-6, Bis(2-oxo-3-oxazolidinyl)phosphinic chloride 77279-24-4 86606-04-4 89032-21-3 89941-07-1, Ethyl 2-piperazinecarboxylate 91142-50-6 101469-92-5 108895-85-8 117439-65-3, Cyclohexaneacetic acid, α-amino-1- **mercapto**- 138542-11-7 161315-62-4 183673-71-4 206550-68-7 211381-51-0 287406-78-4 287406-80-8 287406-81-9 287406-82-0 287406-83-1 287406-95-5 287407-02-7 287407-71-0 287407-95-8 287408-04-2 287408-05-3 287408-06-4 287408-07-5 287408-08-6
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of acetylenic α-amino acid-based sulfonamide hydroxamic acid TACE inhibitors)

L21 ANSWER 14 OF 28 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:475659 HCAPLUS
DOCUMENT NUMBER: **133:104976**
TITLE: 1-Carboxymethyl-2-oxo-azepan derivatives as selective inhibitors of **MMP**-12
INVENTOR(S): Warshawsky, Alan M.; Janusz, Michael J.
PATENT ASSIGNEE(S): Aventis Pharmaceuticals Inc., USA
SOURCE: PCT Int. Appl., 86 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000040577	A1	20000713	WO 1999-US26748	19991112

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU,

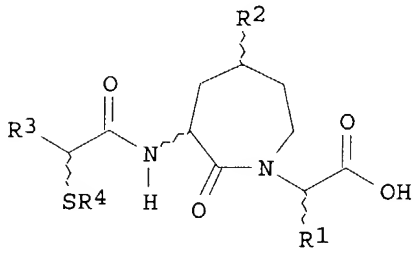
CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL,
IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD,
MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK,
SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY,
KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE,
DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF,
CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

CA 2356689	AA	20000713	CA 1999-2356689	19991112
EP 1150975	A1	20011107	EP 1999-961647	19991112

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, SI, LT, LV, FI, RO

PRIORITY APPLN. INFO.:	US 1998-224457	A	19981231
	WO 1999-US26748	W	19991112

OTHER SOURCE(S): MARPAT 133:104976
GI



I

AB The title compds. [I; R1 = H, alkyl, CH2SCH2NHCOMe, etc.; R2 = alkyl, (CH2)pheteroaryl, (CH2)pAr1 (wherein Ar1 = (un)substituted Ph, naphthyl); R3 = alkyl, (CH2)mW, (CH2)mZQ (W = phthalimido; Z = a bond, O, NR6, etc.; Q = H, (CH2)nY; Y = H, aryl, heteroaryl, etc.); R4 = H, COR7, CO(CH2)qK, SG (K = morpholino, piperidino, pyrrolidino, etc.; G = pyridyl, (CH2)w(pyridyl), etc.); R6 = H, alkyl; R7 = H, alkyl, (CH2)pAr2 (Ar2 = (un)substituted Ph, naphthyl); m = 2-4; n = 0-4; p = 0-2; w = 1-3] were claimed as inhibitors of matrix metalloproteinases (**MMPs**), especially as selective inhibitors of **MMP**-12 (no data for final compds.). Compds. I are claimed to be effective at 1-100 mg/kg/day.

ED Entered STN: 14 Jul 2000

IC ICM C07D403-12
ICS A61K031-55; C07D223-10

CC 27-21 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 1

ST carboxymethyloxoazepan intermediate prepn **MMP12** selective inhibitor

IT 9004-06-2, **MMP** 12
RL: BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study)
(1-carboxymethyl-2-oxo-azepan derivs. as selective inhibitors of **MMP**-12)

IT 60-32-2, 6-Aminohexanoic acid 2916-68-9, 2-(Trimethylsilyl)ethanol 22509-74-6, N-Carbethoxyphthalimide 90719-32-7, (S)-4-Benzyl-2-oxazolidinone 143365-54-2
RL: RCT (Reactant); RACT (Reactant or reagent)
(1-carboxymethyl-2-oxo-azepan derivs. as selective inhibitors of **MMP**-12)

IT 4443-26-9P 5107-16-4P 205391-14-6P 205391-15-7P 205391-16-8P 205391-17-9P 205391-18-0P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(1-carboxymethyl-2-oxo-azepan derivs. as selective inhibitors of **MMP**-12)

IT 205391-19-1P
RL: SPN (Synthetic preparation); PREP (Preparation)
(1-carboxymethyl-2-oxo-azepan derivs. as selective inhibitors of **MMP**-12)

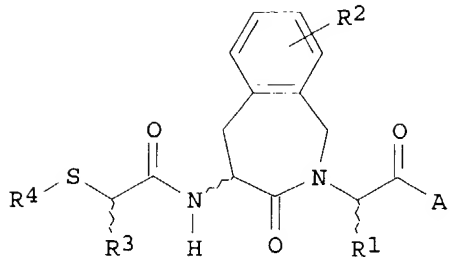
RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Hoechst Marion Roussel	1998			WO 9812211 A	HCAPLUS

L21 ANSWER 15 OF 28 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:475647 HCAPLUS
DOCUMENT NUMBER: **133:104975**
TITLE: Preparation of N-carboxymethyl substituted benzolactams as inhibitors of matrix metalloproteinase
INVENTOR(S): Warshawsky, Alan; Janusz, Michael J.; Flynn, Gary A.
PATENT ASSIGNEE(S): Aventis Pharmaceuticals Inc., USA
SOURCE: PCT Int. Appl., 108 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000040564	A1	20000713	WO 1999-US28339	19991130
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2358955	AA	20000713	CA 1999-2358955	19991130
EP 1150957	A1	20011107	EP 1999-961877	19991130
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
PRIORITY APPLN. INFO.:			US 1998-224549	A 19981231
			WO 1999-US28339	W 19991130

OTHER SOURCE(S): MARPAT 133:104975
GI



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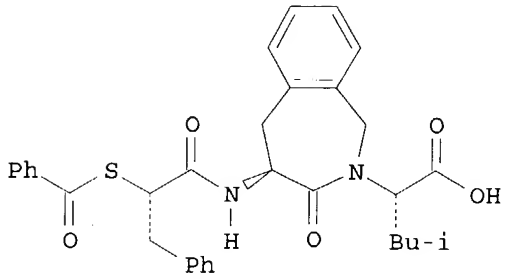


II

AB The title compds. [I; A = OH, NRR' (wherein R, R' = H, alkyl; NRR' = morpholino, piperidino, pyrrolidino, N-isoindolyl); R1 = alkyl, (CH2)4NH2, CH2OH, etc.; R2 = H, halo, alkoxy, etc.; R3 = alkyl, (CH2)mW, (CH2)pAr3, etc. (m = 2-8; p = 0-10; W = phthalimido; Ar3 = pyridyl, thienyl, quinolinyl, etc.); R4 = H, COR10, CO(CH2)qK, SG (R10 = H, alkyl, Ph, CH2Ph; q = 0-2; K = pyridyl, 1-imidazolyl, etc.; G = pyridyl, (CH2)w(pyridyl), etc.; w = 1-3)] which inhibit matrix metallo-proteinases (**MMPs**) (no biol. data) and as such are useful in treating neoplasms, atherosclerosis, and chronic inflammatory diseases, were prepared E.g., a multi-step synthesis of benzolactam II was given. Compds. I are effective at 1-100 mg/kg/day.

ED Entered STN: 14 Jul 2000

IC ICM C07D223-16
ICS C07D403-12; C07K005-06; A61K031-55; A61P011-00; A61P007-00; A61P035-00

CC 27-21 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 1

RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
E R Squibb & Sons Inc	1994			EP 0599444 A	HCAPLUS
Flynn, G	1995			US 5424425 A	HCAPLUS
Flynn, G	1996			US 5491143 A	HCAPLUS
Merrell Dow Pharmaceuti				US 5731306 A	HCAPLUS
Merrell Dow Pharmaceuti	1995			WO 9521839 A	HCAPLUS
Merrell Dow Pharmaceuti	1995			WO 9521854 A	HCAPLUS
The Procter & Gamble Co	1996			WO 9629313 A	HCAPLUS
TourwE, D	1992	2	1305	BIOORGANIC & MEDICIN	HCAPLUS

L21 ANSWER 16 OF 28 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:421113 HCAPLUS
DOCUMENT NUMBER: **133:58802**

TITLE: Preparation of hydroxycarbamoylalkylcarboxylic acid azacyclic hydrazides as TNF-α inhibitors

INVENTOR(S): Broadhurst, Michael John; Johnson, William Henry; Walter, Daryl Simon

PATENT ASSIGNEE(S): F. Hoffmann-La Roche Ag, Switz.

SOURCE: PCT Int. Appl., 128 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

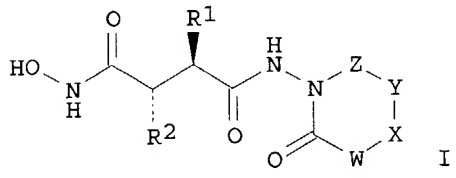
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000035885	A1	20000622	WO 1999-EP9423	19991202
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2353924	AA	20000622	CA 1999-2353924	19991202
BR 9916005	A	20010904	BR 1999-16005	19991202
EP 1137640	A1	20011004	EP 1999-965432	19991202
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
TR 200101644	T2	20011121	TR 2001-200101644	19991202
AU 765729	B2	20030925	AU 2000-20950	19991202
CN 1132819	B	20031231	CN 1999-814323	19991202
US 6281363	B1	20010828	US 1999-457798	19991209
ZA 2001004670	A	20020909	ZA 2001-4670	20010607
PRIORITY APPLN. INFO.:			GB 1998-27408 A	19981211
			GB 1999-25211 A	19991025
			WO 1999-EP9423 W	19991202

OTHER SOURCE(S): MARPAT 133:58802

GI



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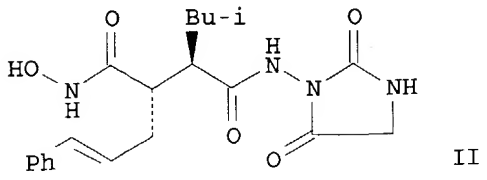

II

AB The title hydrazine derivs. (I) [wherein V = a spacer group; W = O, S, CO,

NR5, (CR3R4)m, or forms a fused ring; X and Y = independently CO, NR5, (CH2)n, or forms a fused ring; Z = CO, CS, SO2, or CH2; R1 = (cyclo)alkyl, alkenyl, cycloalkylalkyl, or aryl(alkyl); R2 = (cyclo)alkyl, alkenyl, cycloalkylalkyl, V-aryl, V-heterocyclyl or (CH2)q-CH=CR8R9; R3, R4, and R5 = independently H, (un)substituted, (cyclo)alkyl, alkenyl, cycloalkylalkyl, aryl(alkyl), hetercyclyl(alkyl), or form a fused ring; R8 and R9 together = alkylene in which a CH2 is optionally replaced by a heteroatom; m = 0 or 1; n = 0-2; q = 1 or 2] and their pharmaceutically acceptable salts were prepared For example, II was formed in a 9-step sequence involving (1-3) preparation of (E)-2(R)-[1(S)-(tert-butoxycarbonyl)-4-phenyl-3-butenyl]-4-methylvalerohydrazide, (4) addition of N-(9-fluorenylmethyloxycarbonyl)glycine, (5) N-deprotection, (6) cycloaddn. with phosgene, (7) deesterification, (8) addition of O-(tetrahydro-2H-pyran-2-yl)hydroxylamine, and (9) O-deprotection. Eighteen invention compds. tested for inhibition of bacterial lipopolysaccharide-induced release of tumor necrosis factor alpha (TNF-α) in THP1 cells displayed IC50 of 147-620 nM. In contrast to structurally related hydroxamic acid derivs., I showed only weak inhibitory activity against the matrix metalloproteinase (**MMP**) family of enzymes, such as collagenases, stromelysins, and gelatinases (no data). I are useful as medicaments, especially in the treatment of inflammatory and autoimmune diseases, osteoarthritis, respiratory diseases, tumors, cachexia, cardiovascular diseases, fever, hemorrhage and sepsis.

ED Entered STN: 23 Jun 2000

IC ICM C07D233-80
ICS A61K031-395; C07D239-54; C07D285-18; C07D495-04; C07D233-34; C07D251-34; C07D249-12; C07D241-08; C07D235-02; C07D233-84; C07D471-10; C07D239-96; C07D401-06; C07D233-96; C07D285-10; C07D487-04; C07D495-04; C07D333-00; C07D239-00

CC 28-9 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1

IT Respiratory tract
(disease, treatment; preparation of hydroxycarbamoylalkylcarboxylic acid azacyclic hydrazides as TNF-α inhibitors by cycloaddn. of (**thio**)phosgene with carboxyalkylcarboxylic acid hydrazides and subsequent treatment with hydroxylamines)

IT Anti-inflammatory agents
Antiarthritics
Antipyretics
Antitumor agents
Cardiovascular agents
(preparation of hydroxycarbamoylalkylcarboxylic acid azacyclic hydrazides as TNF-α inhibitors by cycloaddn. of (**thio**)phosgene with carboxyalkylcarboxylic acid hydrazides and subsequent treatment with hydroxylamines)

IT Hydrazides
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of hydroxycarbamoylalkylcarboxylic acid azacyclic hydrazides as TNF-α inhibitors by cycloaddn. of (**thio**)phosgene with carboxyalkylcarboxylic acid hydrazides and subsequent treatment with hydroxylamines)

IT Tumor necrosis factors
RL: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)
(preparation of hydroxycarbamoylalkylcarboxylic acid azacyclic hydrazides as TNF-α inhibitors by cycloaddn. of (**thio**)phosgene with

carboxyalkylcarboxylic acid hydrazides and subsequent treatment with hydroxylamines)

IT Autoimmune disease
Cachexia
Hemorrhage
Sepsis
(treatment; preparation of hydroxycarbamoylalkylcarboxylic acid azacyclic hydrazides as TNF-α inhibitors by cycloaddn. of (**thio**)phosgene with carboxyalkylcarboxylic acid hydrazides and subsequent treatment with hydroxylamines)

IT 277303-69-2P 277303-71-6P 277303-73-8P 277303-74-9P 277303-76-1P
277303-77-2P 277303-78-3P 277303-79-4P 277303-80-7P 277303-81-8P
277303-82-9P 277303-83-0P 277303-84-1P 277303-85-2P 277303-86-3P
277303-87-4P 277303-88-5P 277303-89-6P 277303-90-9P 277303-91-0P
277303-92-1P 277303-93-2P 277303-94-3P 277303-95-4P 277303-97-6P
277303-98-7P 277303-99-8P 277304-00-4P 277304-01-5P 277304-02-6P
277304-03-7P 277304-04-8P 277304-05-9P 277304-06-0P 277304-07-1P
277304-08-2P 277304-09-3P 277304-11-7P 277304-13-9P 277304-15-1P
277304-17-3P 277304-19-5P 277304-21-9P 277304-23-1P 277304-24-2P
277304-26-4P 277304-27-5P 277304-28-6P 277304-29-7P 277304-30-0P
277304-31-1P 277304-32-2P 277304-33-3P 277304-34-4P 277304-35-5P
277304-36-6P 277304-37-7P 277304-38-8P 277304-39-9P 277304-40-2P
277304-41-3P 277304-42-4P 277304-43-5P 277304-44-6P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of hydroxycarbamoylalkylcarboxylic acid azacyclic hydrazides as TNF-α inhibitors by cycloaddn. of (**thio**)phosgene with carboxyalkylcarboxylic acid hydrazides and subsequent treatment with hydroxylamines)

IT 98-09-9, Benzenesulfonyl chloride 100-63-0, Phenylhydrazine 501-53-1, Benzyl chloroformate 555-96-4, Benzylhydrazine 622-33-3, O-Benzylhydroxylamine 1138-80-3, N-(Benzyloxycarbonyl)glycine 1793-07-3, 2-Methoxycarbonylphenyl isocyanate 2949-22-6, Ethyl isocyanatoacetate 3339-73-9, 3-Phthalimidopropionic acid 4392-24-9, Cinnamyl bromide 4403-36-5, 2-Phthalimidoethanesulfonyl chloride 5331-43-1, Benzyl carbazate 6436-90-4, N-Benzyl glycine ethyl ester 6723-30-4, O-(Tetrahydro-2H-pyran-2-yl)hydroxylamine 14667-47-1, Methyl 2-aminonicotinate 17335-90-9, 2,6-Dioxo-4-morpholinecarboxylic acid benzyl ester 21055-37-8, Methyl 2-**isothiocyanatoacetate** 22288-78-4, Methyl 3-**aminothiophene**-2-carboxylate 29022-11-5, N-(9-Fluorenylmethoxycarbonyl)glycine 30293-85-7 30293-86-8 39570-63-3 40203-94-9 40339-69-3 62402-24-8, N-(2-Pyridylmethyl)glycine ethyl ester 93778-88-2 106366-62-5, Ethyl 1-isocyanato-1-cyclobutanecarboxylate 112245-04-2 114877-91-7 120219-17-2 122246-58-6 123639-56-5 128326-91-0 128421-86-3, N-[2-[[(1,1-Dimethylethoxy)carbonyl]amino]ethyl]glycine methyl ester 129799-08-2 144876-60-8, 2-(Trimethylsilyl)ethyl 1-isocyanato-1-cyclohexanecarboxylate 145080-94-0 145080-95-1 186969-63-1 206761-74-2 253795-93-6 277305-65-4 277305-66-5 277305-67-6 277305-68-7 277305-69-8 277305-70-1 277305-71-2 277305-72-3
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of hydroxycarbamoylalkylcarboxylic acid azacyclic hydrazides as TNF-α inhibitors by cycloaddn. of (**thio**)phosgene with carboxyalkylcarboxylic acid hydrazides and subsequent treatment with hydroxylamines)

IT 189323-10-2P 219614-24-1P 219614-25-2P 219614-39-8P 219615-70-0P
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RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of hydroxycarbamoylalkylcarboxylic acid azacyclic hydrazides as TNF-α inhibitors by cycloaddn. of (**thio**)phosgene with carboxyalkylcarboxylic acid hydrazides and subsequent treatment with hydroxylamines)

RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
F Hoffmann-La Roche Ag	1995			WO 9533709 A	HCAPLUS
F Hoffmann-La Roche Ag	1999			DE 19829229 A	HCAPLUS

L21 ANSWER 17 OF 28 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2000:210116 HCAPLUS

DOCUMENT NUMBER: **132:251070**

TITLE: Preparation and utilization of novel **thiol** derivatives

INVENTOR(S): Yamashita, T[illegible]akizawa, Masayuki; Yoshimura, H[illegible]

PATENT ASSIGNEE(S): Takeda Chemi[illegible]apan

SOURCE: PCT Int. App[illegible]
CODEN: PIXX[illegible]

Applicants

DOCUMENT TYPE: Patent

LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT: 1

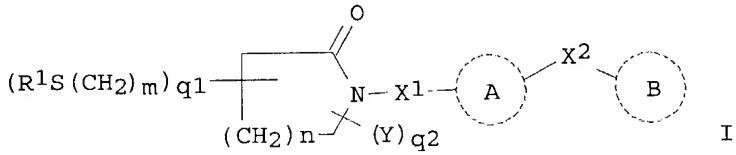
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000017162	A1	20000330	WO 1999-JP5103	19990920
W: AE, AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CR, CU, CZ, DM, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2344412	AA	20000330	CA 1999-2344412	19990920

AU 9956537	A1	20000410	AU 1999-56537	19990920
JP 2000159747	A2	20000613	JP 1999-266295	19990920
EP 1132379	A1	20010912	EP 1999-943412	19990920
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
US 6420415	B1	20020716	US 2001-787623	20010320
US 2003078253	A1	20030424	US 2002-161289	20020603
US 6699881	B2	20040302		
US 2004157894	A1	20040812	US 2004-757325	20040113
PRIORITY APPLN. INFO.:			JP 1998-266037 A	19980921
			WO 1999-JP5103 W	19990920
			US 2001-787623 A3	20010320
			US 2002-161289 A3	20020603

OTHER SOURCE(S): MARPAT 132:251070

GI



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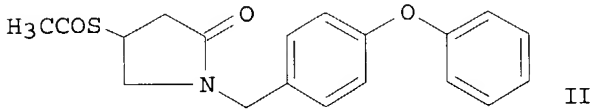

II

AB Title compds [I; wherein the rings A and B represent each an optionally substituted homocycle or heterocycle, etc.; R1s are the same or different and each represents hydrogen, optionally substituted hydrocarbyl, acyl, etc.; X1 represents a bond, optionally substituted divalent aliphatic hydrocarbyl, etc.; X2 represents a bond, optionally substituted divalent aliphatic hydrocarbyl, O, etc.; Ys are the same or different and each represents hydrogen, optionally substituted hydrocarbyl, oxo, etc.; m is 0 or 1; n is an integer of 1 to 3; q1 is an integer of 1 to 2n+4; and q2 is an integer of 0 to 2n+3, provided that q1+q2 is 2n+4], stereoisomers, and salts thereof are prepared and tested as matrix **metalloprotease** inhibitors and are useful as drugs. The title compound (R)-II was prepared and tested.

ED Entered STN: 31 Mar 2000

IC ICM C07D207-26
ICS C07D207-40; C07D211-88; C07D405-12; C07D403-12; C07D401-12; C07D409-12; A61K031-40; A61K031-44; A61K031-445; A61K031-505; A61K031-535; C07M007-00

CC 27-10 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 1, 63

ST phenoxybenzylpyrrolidinedione prepn matrix **metalloprotease** inhibitor; phenoxybenzyl **mercaptopyrrolidinedione** prepn matrix **metalloprotease** inhibitor

IT Arthritis
(acute; preparation of **thiol** derivs. as drug)
IT Gingiva
(disease; preparation of **thiol** derivs. as drug)
IT Eye, disease
(keratopathy, ulcer; preparation of **thiol** derivs. as drug)
IT Antiarthritics
Antitumor agents
(preparation of **thiol** derivs. as drug)
IT Osteoporosis
(therapeutic agents; preparation of **thiol** derivs. as drug)
IT 262286-66-8P 262286-72-6P 262286-75-9P 262286-80-6P 262286-82-8P
262286-86-2P 262286-89-5P 262286-90-8P 262286-92-0P 262286-95-3P
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RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of **thiol** derivs. as matrix **metalloprotease** inhibitors)
IT 262286-67-9P 262286-68-0P 262286-69-1P 262286-70-4P 262286-71-5P
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262864-42-6P 262864-43-7P 262864-45-9P 262864-47-1P 262864-48-2P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use);

BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of **thiol** derivs. as matrix **metalloprotease** inhibitors)

IT 141907-41-7, Matrix **metalloprotease**
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(preparation of **thiol** derivs. as matrix **metalloprotease** inhibitors)

IT 67-36-7, 4-Phenoxybenzaldehyde 98-91-9, **Thiobenzoic** acid 100-52-7, Benzaldehyde, reactions 103-71-9, Phenylisocyanate, reactions 106-48-9 110-78-1, Propylisocyanate 132-64-9, Dibenzofuran 150-30-1, Phenylalanine 328-39-2, Leucine 371-41-5, 4-Fluorophenol 459-57-4 533-31-3, 1,3-Benzodioxol-5-ol 589-15-1, p-Bromobenzyl bromide 590-92-1, 3-Bromopropionic acid 611-95-0, 4-Benzoylbenzoic acid 623-00-7 623-05-2, 4-Hydroxybenzyl alcohol 623-33-6, Glycine ethyl ester hydrochloride 924-49-2, 4-Amino-3-hydroxybutyric acid 1192-30-9, Tetrahydrofurfuryl bromide 1208-87-3 2417-72-3, Methyl 4-(bromomethyl)-benzoate 2491-20-5, L-Alanine methyl ester hydrochloride 3173-56-6, Benzyl isocyanate 5027-16-7 5332-26-3, N-(Bromomethyl)phthalimide 5445-44-3 5466-06-8, 3-**Mercaptopropionic** acid ethyl ester 5551-11-1, 4-Chloro-2-nitrobenzaldehyde 6667-60-3 6908-41-4, Methyl 4-hydroxymethylbenzoate 6953-60-2, S-**Acetylmercaptosuccinic** acid anhydride 7144-05-0, 4-Aminomethylpiperidine 16533-72-5, cis-Epoxysuccinic acid 18600-42-5, 4-Nitrobenzylamine hydrochloride 22677-21-0 25747-41-5, 4-Hydroxy-2-pyrrolidone 27019-47-2, β-Alanine benzyl ester p-toluenesulfonate 36239-09-5, Ethyl-3-chloro-3-oxopropionate 39515-51-0, 3-Phenoxybenzaldehyde 40200-69-9 78456-17-4 85319-59-1 95922-54-6 107622-80-0 118468-18-1 169944-04-1 262862-59-9 262862-60-2 262862-61-3 262862-63-5 262862-71-5 262862-75-9 262864-40-4
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of **thiol** derivs. as matrix **metalloprotease** inhibitors)

IT 836-42-0P, 4-Benzyloxybenzyl chloride 836-43-1P, 4-Benzyloxybenzyl alcohol 1188-33-6P 1892-57-5P, 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide 2215-77-2P, 4-Phenoxybenzoic Acid 3291-46-1P, cis-Epoxysuccinic acid diethyl ester 5619-07-8P, D,L-Phenylalanine methyl ester hydrochloride 6158-54-9P 6322-53-8P, D,L-Leucine methyl ester hydrochloride 14297-39-3P 22494-53-7P 23450-30-8P, Methyl 4-benzylbenzoate 29021-91-8P, 3-Dibenzofurancarboxylic acid 34224-29-8P 34905-00-5P 35714-20-6P, 4-Benzylbenzylalcohol 36602-01-4P 42728-62-1P 56651-56-0P 61343-99-5P 68252-20-0P 71666-05-2P 74004-40-3P 80676-35-3P 87179-81-5P 99419-48-4P 111818-34-9P 124397-37-1P, Methyl 4-phenoxymethylbenzoate 129136-15-8P 137736-06-2P 148776-17-4P, 3-Nitro-4-phenoxybenzaldehyde 167091-96-5P 167091-97-6P 169943-89-9P 194017-71-5P 262861-86-9P 262861-91-6P 262861-92-7P 262862-06-6P 262862-07-7P 262862-08-8P 262862-09-9P 262862-16-8P 262862-17-9P 262862-18-0P 262862-19-1P 262862-20-4P 262862-21-5P 262862-22-6P 262862-23-7P 262862-24-8P 262862-25-9P 262862-26-0P 262862-27-1P 262862-28-2P 262862-29-3P 262862-30-6P 262862-33-9P 262862-34-0P 262862-35-1P 262862-50-0P 262862-51-1P 262862-52-2P 262862-53-3P 262862-54-4P 262862-55-5P 262862-62-4P 262862-64-6P 262862-65-7P 262862-66-8P 262862-67-9P 262862-68-0P 262862-69-1P 262862-70-4P 262862-72-6P 262862-73-7P 262862-74-8P 262862-76-0P 262862-77-1P 262862-78-2P 262862-79-3P 262862-80-6P 262862-81-7P 262862-82-8P 262862-83-9P 262862-84-0P 262862-85-1P 262862-86-2P 262862-87-3P 262862-88-4P 262862-91-9P 262862-92-0P 262862-93-1P 262862-94-2P 262862-95-3P 262862-96-4P 262862-97-5P 262862-98-6P 262862-99-7P

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RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of **thiol** derivs. as matrix **metalloprotease** inhibitors)

IT 59587-94-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(α-Ph N-tert-butyloxycarbonylglutamate; preparation of **thiol** derivs. as matrix **metalloprotease** inhibitors)

RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
F Hoffmann-La Roche Ag				JP 06065196 A	HCAPLUS
F Hoffmann-La Roche Ag				NO 9302117 A	HCAPLUS
F Hoffmann-La Roche Ag				BR 9302273 A	
F Hoffmann-La Roche Ag				FI 9302692 A	
F Hoffmann-La Roche Ag				AU 9339816 A	HCAPLUS
F Hoffmann-La Roche Ag	1993			EP 574758 A1	HCAPLUS
General Electric Compan				GB 1392628 A	HCAPLUS
General Electric Compan				FR 2146253 A1	HCAPLUS
General Electric Compan				DE 2234149 A	HCAPLUS
General Electric Compan				US 3766138 A	HCAPLUS
General Electric Compan				NL 7209825 A	HCAPLUS
General Electric Compan				BE 786120 A1	HCAPLUS
General Electric Compan				IT 962887 A	HCAPLUS
General Electric Compan				CA 982736 A1	HCAPLUS
General Electric Compan	1974			US 3855239 A	HCAPLUS
Thomas, L	1990	29	197	Biopolymers	

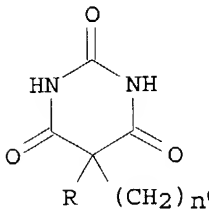
L21 ANSWER 18 OF 28 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:27824 HCAPLUS
DOCUMENT NUMBER: **130:95560**
TITLE: Preparation of barbituric acid derivatives with antimetastatic and antitumor activity
INVENTOR(S): Oliva, Ambrogio; De Cillis, Gianpiero; Grams, Frank; Livi, Valeria; Zimmermann, Gerd; Menta, Ernesto; Krell, Hans-Willi
PATENT ASSIGNEE(S): Boehringer Mannheim G.m.b.H., Germany
SOURCE: PCT Int. Appl., 34 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 9858925	A1	19981230	WO 1998-EP3677		19980618
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG					
AU 9885391	A1	19990104	AU 1998-85391		19980618
AU 746853	B2	20020502			
EP 989982	A1	20000405	EP 1998-936361		19980618
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, SI, LT, LV, FI, RO					
TR 9903148	T2	20000421	TR 1999-9903148		19980618
BR 9810450	A	20000905	BR 1998-10450		19980618
JP 2002504916	T2	20020212	JP 1999-503748		19980618
ZA 9805352	A	19991220	ZA 1998-5352		19980619
MX 9911992	A	20000630	MX 1999-11992		19991217
US 6335332	B1	20020101	US 2000-445461		20000403
PRIORITY APPLN. INFO.:			EP 1997-110200	A	19970621
			WO 1998-EP3677	W	19980618

OTHER SOURCE(S): MARPAT 130:95560

GI



I

AB The title compds. [I; R = WV; A = R1, NR2(CH2)mNR9TR10, etc.; R1 = OH, C1-4 alkoxy, NH2, mono- or di(C1-4 alkyl)amino, (un)substituted phenoxy, benzyloxy, etc.; R9, R10 = H, (un)substituted C1-4 alkyl, Ph, etc.; R9R10NCO may form a 5- or 6-membered lactam ring; T = CO, SO2; V = (un)substituted (un)saturated mono- or bicyclic group optionally containing 1-3 N, O, S; W = bond, C1-8 alkyl, C2-8 alkenyl; n = 1-3] as enantiomers, racemates, diastereoisomers, tautomers or their mixts., and their pharmaceutically acceptable salts, inhibitors of the metzincins useful for the title purpose, were prepared For example, cyclocondensation of urea with di-Et 2-octylmalonate (preparation by alkylation of di-Et malonate with 1-bromooctane given) gave 5-octylbarbituric acid which was alkylated with BrCH2CO2Et in DMF in the presence of Na2CO3 to give 5-octyl-5-(ethoxycarbonylmethyl)barbituric acid. The latter in vitro inhibited human neutrophil collagenase (**MMP**-8) with IC50 107 nM and gelatinase 92 kD (**MMP**-9) with IC50 19.6 nM which gave selectivity (**MMP**-9/**MMP**-8) ratio of 0.18-0.2, vs. 0.93 for batimastat as a reference Approx. 6 I were prepared and approx. 21 I were claimed.

ED Entered STN: 14 Jan 1999

IC ICM C07D401-12
ICS C07D239-62; C07D403-12; A61K031-515

CC 28-16 (Heterocyclic Compounds (More Than One Hetero Atom))

Section cross-reference(s): 1

RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Abbott	1991			EP 0457213 A	HCAPLUS
Adamczyk, M	1997	8	281	Bioconjugate Chemist	HCAPLUS
Al Sharifi, M	1982	34	126	J Pharm Pharmacol	HCAPLUS
Al Sharifi, M	1982		13	THE EFFECT OF ANTIAM	HCAPLUS
Haskins, N	1974	6	181	Adv Mass Spectrom	HCAPLUS
Haskins, N	1975		3	QUALITAT AND QUANTIT	HCAPLUS
Pharm, J	1991	46	293	CHROMIC OXYDATION AN	
Sloan-Kettering Instit	1991			WO 9108191 A	
Talab, A	1992			CHROMIC OXYDATION AN	HCAPLUS
Tecilla, P	1995	51	435	Tetrahedron	HCAPLUS

L21 ANSWER 19 OF 28 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:197516 HCAPLUS
DOCUMENT NUMBER: **128:270870**
TITLE: Preparation of 3-**mercaptoacetylamino**-1,5-substituted-2-azepinone derivatives as matrix metalloproteinase inhibitors
INVENTOR(S): Warshawsky, Alan M.; Flynn, Gary A.; Patel, Meena V.; Beight, Douglas W.; Burkhart, Joseph P.; Tsay, Jiu-Tsair; Janusz, Michael J.; Shen, Jian; Dharanipragada, Ramalinga M.
PATENT ASSIGNEE(S): Hoechst Marion Roussel, Inc., USA
SOURCE: PCT Int. Appl., 160 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9812211	A1	19980326	WO 1997-US13738	19970804
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2266759	AA	19980326	CA 1997-2266759	19970804
AU 9738278	A1	19980414	AU 1997-38278	19970804
AU 718055	B2	20000406		
EP 928291	A1	19990714	EP 1997-935308	19970804
EP 928291	B1	20021204		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
CN 1234039	A	19991103	CN 1997-199024	19970804
BR 9713207	A	20000404	BR 1997-13207	19970804
NZ 334490	A	20000825	NZ 1997-334490	19970804
JP 2001501926	T2	20010213	JP 1998-514658	19970804
AT 229034	E	20021215	AT 1997-935308	19970804
PT 928291	T	20030331	PT 1997-935308	19970804
ES 2184126	T3	20030401	ES 1997-935308	19970804
TW 445262	B	20010711	TW 1997-86113339	19970913

ZA 9708307	A	19980319	ZA 1997-8307		19970915
MX 9902577	A	20000131	MX 1999-2577		19990317
NO 9901316	A	19990518	NO 1999-1316		19990318
KR 2000036246	A	20000626	KR 1999-702336		19990318
HK 1020741	A1	20030502	HK 1999-105993		19991221
PRIORITY APPLN. INFO.:			US 1996-719291	A	19960919
			WO 1997-US13738	W	19970804

OTHER SOURCE(S): MARPAT 128:270870
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The present invention relates to certain novel title compds. I [R1 = C1-6 alkyl, W-(CH2)m, Q-Z-(CH2)m; W = phthalimido; Z = bond, O, NR6, CONR6, NR6CO, NHCONR6, O2CNR6, NHCO2, SO2NR6; Q = H, Y-(CH2)n; Y = H, C6-10 aryl, C3-9 heteroaryl, CO2R6, NR62, morpholino, piperidino, pyrrolidino, isoindolyl; R2 = C1-4 alkyl, (CH2)p-(C3-9) heteroaryl, (CH2)p-Ar1; Ar1 = (un)substituted Ph or naphthyl; R3 = H, C1-6 alkyl, CH2SCH2NHAc, (CH2)p-A, (CH2)m-B, CH2-D-R7; A = C6-10 aryl, C3-9 heteroaryl, cyclohexyl; B = NR72, guanidino, nitroguanidino, CO2R6, CONR6; D = O, S; R4 = H, (CH2)m-S(O)pX1(R6)2; R5 = H, C1-6 alkyl; NR4R5 = piperidino, pyrrolidino, isoindolyl; R6 = H, C1-6 alkyl; R7 = H, C1-4 alkyl, (CH2)p-Ar1; R8 = H, CO2R7, CO(CH2)q-K, S-G; K = nitrogen-containing heterocycle, NR9R10; G = substituted alkyl; R9, R10 = independently C1-4 alkyl, (CH2)p-Ar1; X, X1 = independently CH, N; m = 2-4; n = 0-4; p = 0-2; q = 0-5] as matrix metalloproteinase inhibitors. Pharmaceutical compns. containing said compds. as well as methods of treating various disease states responding to inhibition of matrix metalloproteinase are also claimed herein. Thus, reductive alkylation of H-L-Phe-NHMe.HCl with azido aldehyde II (prepared in 5 steps from 4-phenylcyclohexanone), followed by deesterification and cyclization gave cis azepine III and its corresponding trans isomer in a 4:5 ratio. Reduction of III with 1,3-**propanedithiol** gave the corresponding amine, which was coupled with 2-bromo-6-phthalimidohexanoic acid to give bromide IV (R = Br). Substitution of IV (R = Br) with p-methoxybenzyl **mercaptan** followed by deprotection gave title compound IV (R = SH) (MDL 108,180). MDL 108,180 inhibited matrix metalloproteinases **MMP**-2, **MMP**-3, and **MMP**-12 in vitro with Ki = 1.2 nM, 39 nM, and 18 nM, resp.

ED Entered STN: 06 Apr 1998

IC ICM C07K005-078
ICS A61K038-05

CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1, 63

ST **mercaptoacetylaminoazepinone** prepn matrix metalloproteinase inhibitor; MDL 108180 106540 matrix metalloproteinase inhibitor; azepinone **mercaptoacetylamino** prepn matrix metalloproteinase inhibitor

IT Antiarteriosclerotics
(antiatherosclerotics; preparation of substituted (**mercaptoacetylamino**)azepinone derivs. as matrix metalloproteinase inhibitors)

IT Lung, disease
(chronic obstructive, obstructive; preparation of substituted (**mercaptoacetylamino**)azepinone derivs. as matrix metalloproteinase inhibitors)

IT Eye, disease
Eye, disease
Eye, disease

(cornea, ulcer; preparation of substituted (**mercaptoacetylamino**)azepinone derivs. as matrix metalloproteinase inhibitors)

IT Periodontium
(disease; preparation of substituted (**mercaptoacetylamino**)azepinone derivs. as matrix metalloproteinase inhibitors)

IT Gingiva
(gingivitis; preparation of substituted (**mercaptoacetylamino**)azepinone derivs. as matrix metalloproteinase inhibitors)

IT Anti-inflammatory agents
Osteoarthritis
Rheumatoid arthritis
(preparation of substituted (**mercaptoacetylamino**)azepinone derivs. as matrix metalloproteinase inhibitors)

IT Multiple sclerosis
(therapeutic agents; preparation of substituted (**mercaptoacetylamino**)azepinone derivs. as matrix metalloproteinase inhibitors)

IT 79955-99-0, Matrix metalloproteinase-3
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(activated; preparation of substituted (**mercaptoacetylamino**)azepinone derivs. as matrix metalloproteinase inhibitors)

IT 205391-09-9P 205391-10-2P 205391-11-3P 205391-12-4P 205391-13-5P 205496-75-9P, MDL 108180 205496-76-0P, MDL 106540
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of substituted (**mercaptoacetylamino**)azepinone derivs. as matrix metalloproteinase inhibitors)

IT 9004-06-2, Matrix metalloproteinase-12 146480-35-5, Matrix metalloproteinase-2
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(preparation of substituted (**mercaptoacetylamino**)azepinone derivs. as matrix metalloproteinase inhibitors)

IT 141907-41-7, Matrix metalloproteinase
RL: BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study)
(preparation of substituted (**mercaptoacetylamino**)azepinone derivs. as matrix metalloproteinase inhibitors)

IT 194934-74-2P
RL: BYP (Byproduct); PREP (Preparation)
(preparation of substituted (**mercaptoacetylamino**)azepinone derivs. as matrix metalloproteinase inhibitors)

IT 60-32-2, 6-Aminocaproic acid 107-11-9, Allylamine 584-93-0, 2-Bromopentanoic acid 589-92-4, 4-Methylcyclohexanone 4894-75-1, 4-Phenylcyclohexanone 6258-60-2, p-Methoxybenzyl **mercaptan** 13734-34-4 13734-41-3 22509-74-6, N-(Ethoxycarbonyl)phthalimide 90719-32-7, (S)-4-Benzyl-2-oxazolidinone 98541-64-1 205391-40-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of substituted (**mercaptoacetylamino**)azepinone derivs. as matrix metalloproteinase inhibitors)

IT 4443-26-9P 5107-16-4P 131451-47-3P 155387-85-2P 194934-72-0P 194934-75-3P 205391-14-6P 205391-15-7P 205391-16-8P 205391-17-9P 205391-18-0P 205391-19-1P 205391-20-4P 205391-21-5P 205391-22-6P 205391-23-7P 205391-24-8P 205391-25-9P 205391-26-0P 205391-27-1P 205391-28-2P 205391-30-6P 205391-31-7P 205391-32-8P 205391-33-9P 205391-34-0P 205391-35-1P 205391-36-2P 205391-37-3P 205391-38-4P 205391-39-5P 205391-41-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of substituted (**mercaptoacetylamino**)azepinone derivs. as matrix metalloproteinase inhibitors)

RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Burkholder, E	1993	3	231	BIOORG MED CHEM LETT	
Chiroscience Ltd	1996			WO 9611209 A	HCAPLUS
Kanebo Ltd	1995			JP 07304746 A	HCAPLUS
Procter & Gamble	1996			WO 9629313 A	HCAPLUS
Res Corp Technologies I	1988			WO 8806890 A	HCAPLUS

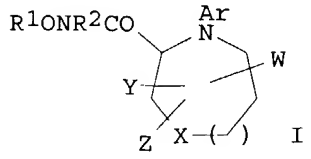
L21 ANSWER 20 OF 28 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:163575 HCAPLUS
DOCUMENT NUMBER: **128:204913**
TITLE: Preparation of thiazepinecarboxamide derivatives and related heterocycles as **metalloprotease** inhibitors
INVENTOR(S): De, Biswanath; Natchus, Michael George; Pikul, Stanislaw; Almstead, Neil Gregory; Matthews, Randall Stryker; Taiwo, Yetunde Olabisi; Cheng, Menyan
PATENT ASSIGNEE(S): Procter & Gamble Company, USA
SOURCE: PCT Int. Appl., 62 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9808827	A1	19980305	WO 1997-US14551	19970822
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2264045	AA	19980305	CA 1997-2264045	19970822
AU 9741529	A1	19980319	AU 1997-41529	19970822
AU 731319	B2	20010329		
EP 925287	A1	19990630	EP 1997-939442	19970822
EP 925287	B1	20030115		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
CN 1228773	A	19990915	CN 1997-197541	19970822
CN 1232457	A	19991020	CN 1997-198547	19970822
BR 9713185	A	19991103	BR 1997-13185	19970822
JP 2000515166	T2	20001114	JP 1998-511711	19970822
NZ 334252	A	20001124	NZ 1997-334252	19970822
AT 231132	E	20030215	AT 1997-939442	19970822
US 6166005	A	20001226	US 1997-921953	19970826
ZA 9707694	A	19980223	ZA 1997-7694	19970827
ZA 9707695	A	19980223	ZA 1997-7695	19970827
NO 9900839	A	19990428	NO 1999-839	19990222
KR 2000035917	A	20000626	KR 1999-701653	19990227
KR 2000035923	A	20000626	KR 1999-701659	19990227
US 6545038	B1	20030408	US 2000-707212	20001106
US 2003186958	A1	20031002	US 2003-361115	20030206

PRIORITY APPLN. INFO.:

US 1996-24764P	P 19960828
WO 1997-US14551	W 19970822
US 1997-921953	A3 19970826
US 2000-707212	A3 20001106

OTHER SOURCE(S): MARPAT 128:204913
GI



AB I [R1 = H; R2 = H, alkyl, acyl; Ar = COR3, SO2R4; R3 = alkoxy, alkyl, aryl, etc.; R4 = alkyl, heteroalkyl, aryl, heteroaryl; X = CH2, O, S, SO, SO2, NR5; R5 = H, alkyl, etc.; W = H, alkyl, alkylene or arylene or heteroarylene bridge between two carbons; Y = H, OH, amino, etc.; Z = -, H, spiro moiety, oxo; n = 1-3], inhibitors of **metalloproteases** (no data), were prepared. E.g., N-hydroxy-2,2-dimethyl-S,S-dioxo-4-[(4-methoxyphenyl)sulfonyl]thiazepine-3(S)-carboxamide was prepared using D-penicillamine and 4-methoxybenzenesulfonyl chloride as starting materials.

ED Entered STN: 19 Mar 1998

IC ICM C07D243-08
ICS C07D267-10; C07D281-04; C07D281-18; A61K031-53; A61K031-54

CC 28-22 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1, 27, 63

ST thiazepinecarboxamide sulfonyl prepn **metalloprotease** inhibitor

IT 204129-53-3P 204129-54-4P 204129-55-5P 204129-56-6P 204129-57-7P
204129-58-8P 204129-59-9P 204129-60-2P 204129-61-3P 204129-62-4P
204129-63-5P 204129-64-6P 204129-65-7P 204129-66-8P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of thiazepinecarboxamide derivs. and related heterocycles as **metalloprotease** inhibitors)

IT 81669-70-7, **Metalloprotease**
RL: BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study)
(preparation of thiazepinecarboxamide derivs. and related heterocycles as **metalloprotease** inhibitors)

IT 52-67-5, D-Penicillamine 98-58-8, 4-Bromobenzenesulfonyl chloride 98-68-0, 4-Methoxybenzenesulfonyl chloride 110-93-0 630-19-3, Trimethylacetaldehyde 1138-56-3, 4-Butoxybenzenesulfonyl chloride 1655-07-8 5259-98-3, 5-Chloro-1-pentanol 70361-61-4, D-**Cysteine** methyl ester hydrochloride 113428-57-2 139937-37-4
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of thiazepinecarboxamide derivs. and related heterocycles as **metalloprotease** inhibitors)

IT 53067-23-5P 71135-95-0P 150989-18-7P 150989-20-1P 150989-21-2P
151062-55-4P 204129-67-9P 204129-68-0P 204129-69-1P 204129-70-4P
204129-71-5P 204129-72-6P 204129-73-7P 204129-74-8P 204129-75-9P
204129-76-0P 204129-77-1P 204129-78-2P 204129-79-3P 204129-80-6P
204129-81-7P 204129-82-8P 204129-83-9P 204129-84-0P 204129-85-1P
204129-86-2P 204129-87-3P 204129-88-4P 204129-89-5P 204129-90-8P
204129-91-9P 204129-92-0P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of thiazepinecarboxamide derivs. and related heterocycles as **metalloprotease** inhibitors)

RETABLE

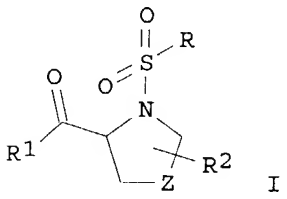
Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Agouron Pharmaceuticals	1997			WO 9720824 A	HCAPLUS
Ciba-Geigy	1996			WO 9600214 A	HCAPLUS
F Hoffmann-La Roche Ag	1995			WO 9533731 A	HCAPLUS
Robl, J	1994	4	1795	BIOORGANIC & MEDICIN	HCAPLUS
The Procter & Gamble Co	1996			WO 9620918 A	HCAPLUS
The Procter & Gamble Co	1996			WO 9629313 A	HCAPLUS

L21 ANSWER 21 OF 28 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:163563 HCAPLUS
DOCUMENT NUMBER: **128:217281**
TITLE: Preparation and formulation of 1-arylsulfonylpyrrolidine-2-carboxylates as **metalloprotease** inhibitors
INVENTOR(S): Natchus, Michael George; De, Biswanath; Pikul, Stanislaw; Almstead, Neil Gregory; Bookland, Roger Gunnard; Taiwo, Yetunde Olabisi; Cheng, Menyan
PATENT ASSIGNEE(S): Procter & Gamble Company, USA
SOURCE: PCT Int. Appl., 86 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9808815	A1	19980305	WO 1997-US14555	19970822
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2263928	AA	19980305	CA 1997-2263928	19970822
AU 9740741	A1	19980319	AU 1997-40741	19970822
AU 741893	B2	20011213		
EP 927161	A1	19990707	EP 1997-938412	19970822
EP 927161	B1	20021016		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
CN 1232451	A	19991020	CN 1997-198539	19970822
BR 9713465	A	20000328	BR 1997-13465	19970822
NZ 334256	A	20001124	NZ 1997-334256	19970822
JP 2000516955	T2	20001219	JP 1998-511715	19970822
JP 3541043	B2	20040707		
AT 226193	E	20021115	AT 1997-938412	19970822
PT 927161	T	20031231	PT 1997-938412	19970822
RU 2221782	C2	20040120	RU 1999-106522	19970822
ES 2201318	T3	20040316	ES 1997-938412	19970822
ZA 9707698	A	19980223	ZA 1997-7698	19970827
NO 9900855	A	19990423	NO 1999-855	19990223

KR 2000035922	A	20000626	KR 1999-701658		19990227
HK 1020962	A1	20030808	HK 2000-100036		20000104
JP 2004115531	A2	20040415	JP 2003-384116		20031113
PRIORITY APPLN. INFO.:			US 1996-24842P	P	19960828
			JP 1998-511715	A3	19970822
			WO 1997-US14555	W	19970822

OTHER SOURCE(S): MARPAT 128:217281
GI



I

AB Title compds. [I; R = alkyl, (hetero)aryl, etc.; R1 = OH, alkoxy, NHOH, alkoxyamino; R2 = ≥1 of OH, alkyl, alkoxy, (hetero)aryl, etc.; Z = (CH2)1-3] were prepared as **metalloprotease** inhibitors (no data). Thus, cis-hydroxy-D-proline was N-acylated by 4-(MeO)C6H4SO2Cl and the esterified product amidated by N2NOK to give (2R,4S)-I [R = C6H4(OMe)-4, R1 = NHOH, R2 = H, Z = CH(OH)].

ED Entered STN: 19 Mar 1998

IC ICM C07D207-48
ICS A61K031-40; C07D417-04; C07D403-04; C07D401-04; C07D403-12; C07D401-12; C07D409-14; C07D413-14; C07D405-12

CC 27-10 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 1, 34, 63

ST arylsulfonylpyrrolidinecarboxylate prepn **metalloprotease** inhibitor

IT Cachexia
Musculoskeletal diseases
(treatment; preparation and formulation of 1-arylsulfonylpyrrolidine-2-carboxylates as **metalloprotease** inhibitors)

IT 81669-70-7, **Metalloprotease**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(mediated disorders; treatment; preparation and formulation of 1-arylsulfonylpyrrolidine-2-carboxylates as **metalloprotease** inhibitors)

IT 204071-36-3P 204071-38-5P 204071-40-9P 204071-42-1P 204071-43-2P
204071-44-3P 204071-45-4P 204071-46-5P 204071-47-6P 204071-48-7P
204071-49-8P 204071-50-1P 204071-51-2P 204071-52-3P 204071-53-4P
204071-54-5P 204071-55-6P 204071-56-7P 204071-57-8P 204071-58-9P
204071-59-0P 204071-60-3P 204071-61-4P 204071-62-5P 204071-63-6P
204071-64-7P 204071-65-8P 204071-66-9P 204071-67-0P 204071-68-1P
204071-69-2P 204071-70-5P 204071-71-6P 204071-72-7P 204071-73-8P
204071-74-9P 204071-75-0P 204071-76-1P 204071-77-2P 204071-78-3P
204071-79-4P 204071-80-7P 204071-81-8P 204071-82-9P 204071-83-0P
204071-84-1P 204071-85-2P 204071-86-3P 204071-87-4P 204071-88-5P
204071-89-6P 204071-90-9P 204071-91-0P 204071-92-1P 204071-93-2P
204071-94-3P 204071-95-4P 204071-96-5P 204071-97-6P 204071-98-7P
204071-99-8P 204072-00-4P 204072-01-5P 204072-02-6P 204072-03-7P
204072-04-8P 204072-05-9P 204072-06-0P 204072-07-1P 204072-08-2P
204072-09-3P 204072-10-6P 204072-11-7P 204072-12-8P 204072-14-0P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological

study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation and formulation of 1-arylsulfonylpyrrolidine-2-carboxylates as **metalloprotease** inhibitors)

IT 60-56-0, 2-**Mercapto**-1-methylimidazole 65-85-0, Benzoic acid, reactions 77-71-4, 5,5-DiMethylhydantoin 98-58-8, 4-Bromobenzenesulfonyl chloride 98-68-0, 4-Methoxybenzenesulfonyl chloride 100-39-0, Benzyl bromide 100-58-3, Phenylmagnesium bromide 101-18-8, 3-Hydroxydiphenylamine 103-16-2, 4-Benzyloxyphenol 108-95-2, Phenol, reactions 108-98-5, **Thiophenol**, reactions 109-00-2, 3-Hydroxypyridine 111-26-2, 1-Hexanamine 111-30-8, Glutaric dialdehyde 122-78-1, Phenylacetaldehyde 123-38-6, Propionaldehyde, reactions 142-61-0, Hexanoyl chloride 149-30-4, 2-**Mercaptobenzothiazole** 500-22-1, 3-Pyridinecarboxaldehyde 616-04-6, 1-Methylhydantoin 696-63-9, 4-**MethoxyThiophenol** 1138-56-3, 4-Butoxybenzenesulfonyl chloride 1499-56-5 1623-92-3, 4-Phenoxybenzenesulfonyl chloride 1806-26-4, 4-n-Octylphenol 2584-71-6, cis-4-Hydroxy-D-proline 3587-60-8, Benzyl chloromethyl ether 3970-21-6, 2-Methoxyethoxymethyl chloride 5414-19-7, Bis(2-bromoethyl) ether 6482-24-2, 2-Bromoethyl methyl ether 7326-19-4 7617-67-6 14002-51-8, [1,1'-Biphenyl]-4-carbonyl chloride 15570-12-4, 3-**MethoxyThiophenol** 16271-33-3, 2,4-Dichlorobenzenesulfonyl chloride 18092-54-1, 2-Nitro-4-methoxybenzenesulfonyl chloride 23095-31-0, 3,4-Dimethoxybenzenesulfonyl chloride 40856-73-3 51212-37-4, trans-3-Phenylproline 81102-38-7 100836-85-9 114676-47-0 137049-00-4 139937-37-4, 2-Methyl-4-Bromobenzenesulfonyl chloride
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation and formulation of 1-arylsulfonylpyrrolidine-2-carboxylates as **metalloprotease** inhibitors)

IT 1138-54-1P 57850-07-4P 182937-63-9P 203934-42-3P 203934-63-8P 203994-66-5P 203994-80-3P 203994-82-5P 204072-15-1P 204072-16-2P 204072-17-3P 204072-18-4P 204072-19-5P 204072-20-8P 204072-21-9P 204072-22-0P 204072-23-1P 204072-24-2P 204072-25-3P 204072-26-4P 204072-27-5P 204072-28-6P 204072-29-7P 204072-30-0P 204072-31-1P 204072-32-2P 204072-34-4P 204072-36-6P 204072-37-7P 204072-38-8P 204072-39-9P 204072-40-2P 204072-41-3P 204072-42-4P 204072-43-5P 204072-44-6P 204072-45-7P 204072-46-8P 204072-47-9P 204072-49-1P 204072-50-4P 204072-51-5P 204072-52-6P 204072-53-7P 204072-54-8P 204072-55-9P 204072-56-0P 204072-57-1P 204072-58-2P 204072-59-3P 204072-60-6P 204072-61-7P 204072-62-8P 204072-63-9P 204072-64-0P 204072-65-1P 204072-66-2P 204072-67-3P 204072-68-4P 204072-69-5P 204072-70-8P 204072-71-9P 204072-72-0P 204072-73-1P 204072-74-2P 204072-75-3P 204072-76-4P 204072-77-5P 204072-78-6P 204072-79-7P 204072-80-0P 204072-81-1P 204072-82-2P 204072-83-3P 204072-84-4P 204072-85-5P 204072-86-6P 204072-87-7P 204072-88-8P 204072-89-9P 204072-90-2P 204072-91-3P 204072-92-4P 204072-93-5P 204072-94-6P 204072-95-7P 204072-96-8P 204072-97-9P 204072-98-0P 204072-99-1P 204073-00-7P 204073-01-8P 204073-02-9P 204073-03-0P 204073-04-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and formulation of 1-arylsulfonylpyrrolidine-2-carboxylates as **metalloprotease** inhibitors)

RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Agouron Pharmaceuticals	1997			WO 9720824 A	HCAPLUS
Andreatta, R	1967	20	1493	AUST J CHEM	HCAPLUS
Bristol-Myers Co	1988			WO 8802627 A	HCAPLUS
Ciba-Geigy Ag	1994			EP 0606046 A	HCAPLUS

Edwards, M	1996	28	193	ORG PREP, PROCED INT	
Fournier Industrie	1997			WO 9724349 A	HCAPLUS
Heintzelman, G	1996	61	4594	J ORG CHEM	
Herdeis, C	1992	325	419	ARCH PHARM (WEINHEIM	HCAPLUS
Hudson, C	1968	21	769	AUST J CHEM	HCAPLUS
Kahl, J	1981		1445	LIEBIGS ANN CHEM	HCAPLUS
Ono Pharmaceutical Co	1997			EP 0769498 A	HCAPLUS
Pfizer Inc	1996			WO 9633172 A	HCAPLUS
Sanofi	1997			WO 9725315 A	HCAPLUS

L21 ANSWER 22 OF 28 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:112235 HCAPLUS
DOCUMENT NUMBER: **128:192934**
TITLE: Preparation of peptide β-sheet mimetics as protease and kinase inhibitors and as inhibitors of transcription factors
INVENTOR(S): Kahn, Michael; Qabar, Maher Nicola; McMillan, Michael Kim; Ogbu, Cyprian Okwara; Eguchi, Masakatsu; Kim, Hwa-ok; Boatman, Patrick Douglas, Jr.; Urban, Jan; et al.
PATENT ASSIGNEE(S): Molecumetics Ltd., USA
SOURCE: PCT Int. Appl., 250 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9805333	A1	19980212	WO 1997-US13622	19970805
W: AL, AM, AT, AU, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2262900	AA	19980212	CA 1997-2262900	19970805
AU 9739058	A1	19980225	AU 1997-39058	19970805
AU 732174	B2	20010412		
EP 915700	A1	19990519	EP 1997-936371	19970805
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
NZ 334227	A	20001027	NZ 1997-334227	19970805
JP 2001524931	T2	20011204	JP 1998-508118	19970805
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US 6117896	A	20000912	US 1998-22934	19980212
NO 9900522	A	19990330	NO 1999-522	19990204
KR 2000029838	A	20000525	KR 1999-700994	19990205
US 6372744	B1	20020416	US 2000-501052	20000209
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US 2004230035	A1	20041118	US 2003-745471	20031222

PRIORITY APPLN. INFO.:

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WO 1997-US13622	W 19970805
US 1998-9665	A3 19980120
US 1998-22934	A3 19980212
US 2000-501052	A1 20000209
US 2000-561107	A1 20000428

OTHER SOURCE(S): MARPAT 128:192934
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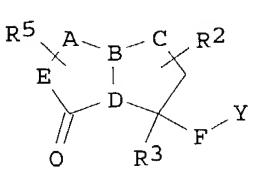

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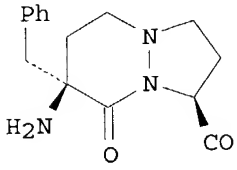


CO-L-Arg-CH_2Cl II

AB β-Sheet mimetics I [A = CO, (CH2)0-4, CO(CH2)1-3, (CH2)1-2CO, (CH2)1-2S; B = N, CH; C = CO, CO(CH2)1-3, (CH2)0-3, O, S, O(CH2)1-2, S(CH2)1-2; D = N, CR4; E = CR1NHZ, NZ, CR1Z; F = bond, CO; R1, R2, R4, R5 = independently amino acid side chain or derivative thereof; R2 = amino acid side chain or derivative thereof, or taken with C forms a fused substituted or unsubstituted homocyclic or heterocyclic ring; R3 = amino acid side chain or derivative thereof, or taken with C forms a bridging moiety (CH2)1-2, O, S; Y, Z represent the remainder of the mol., with the proviso that any two adjacent CH groups of the bicyclic ring may form a double bond] and methods relating to the same are disclosed. The β-sheet mimetics have utility as protease and kinase inhibitors, as well as inhibitors of transcription factors. Methods of the invention include administration of a β-sheet mimetic, or use of the same for the manufacture of a medicament for treatment of a variety of conditions associated with the targeted protease, kinase and/or transcription factor. Thus, bicyclic peptide mimic II was prepared in several steps from phenylalanine Me ester, Et acrylate, and a protected arginine chloromethyl ketone derivative II was tested for inhibitory activity against a variety of serine proteases, and showed IC50 = 1.2 nM against thrombin in an in vitro assay.

ED Entered STN: 25 Feb 1998

IC ICM A61K031-50
ICS A61K031-435; A61K031-415; A61K031-40; A61K038-00

CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1

IT **Thioredoxins**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(preparation of peptide β-sheet mimetics as protease and kinase inhibitors and as inhibitors of transcription factors)

IT 9001-01-8, Kallikrein 9001-28-9, Factor IX 9013-55-2, Blood-coagulation factor XI 9026-43-1, Serine kinase 9031-44-1, Kinase 37205-61-1, Protease inhibitor 37259-58-8, Serine protease 37353-41-6, **Cysteine** protease 78169-47-8, Aspartic protease 80449-02-1, Tyrosine kinase 81669-70-7, **Metalloprotease** 97501-93-4, Tryptase
RL: BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study)
(preparation of peptide β-sheet mimetics as protease and kinase inhibitors and as inhibitors of transcription factors)

IT 55-81-2, p-Methoxyphenethylamine 56-86-0, L-Glutamic acid, reactions

62-53-3, Benzenamine, reactions 64-04-0, Phenethylamine 78-85-3, Methacrolein 95-16-9, Benzothiazole 100-52-7, Benzaldehyde, reactions 140-88-5 156-41-2, p-Chlorophenethylamine 288-47-1, Thiazole 569-51-7, 1,2,3-Benzenetricarboxylic acid 619-44-3, Methyl 4-iodobenzoate 626-99-3, 2,4-Pentadienoic acid 868-59-7, L-**Cysteine** ethyl ester hydrochloride 922-67-8, Methyl propiolate 2605-67-6, Methyl (triphenylphosphoranylidene)acetate 2696-85-7, 2-Butylaniline 2987-16-8, 3,3-Dimethylbutyraldehyde 3300-51-4 4336-70-3, Cyanomethyltriphenylphosphonium chloride 5418-86-0, Tris(**methylthio**)methane 5680-86-4 6294-89-9, Methyl hydrazinocarboxylate 7524-50-7, L-Phenylalanine methyl ester hydrochloride 10236-14-3 15988-11-1, 4-Phenylurazole 17102-64-6, Sorbinol 18598-63-5, L-**Cysteine** methyl ester hydrochloride 20577-61-1, Methyl 2,4-dioxopentanoate 20849-78-9, 4-(2-Chloroethyl)benzoic acid 71989-26-9 73506-81-7, Hexadienal 92136-39-5 102185-38-6 122235-70-5 183442-86-6 183443-14-3 183443-41-6 203453-89-8

RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of peptide β-sheet mimetics as protease and kinase inhibitors and as inhibitors of transcription factors)

RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Molecumetics Ltd	1996			WO 9630035 A	HCAPLUS
Molecumetics Ltd	1996			WO 9630035 A	HCAPLUS
Scola	1997			WO 9705160 A	HCAPLUS
Scola	1997			WO 9705160 A	HCAPLUS

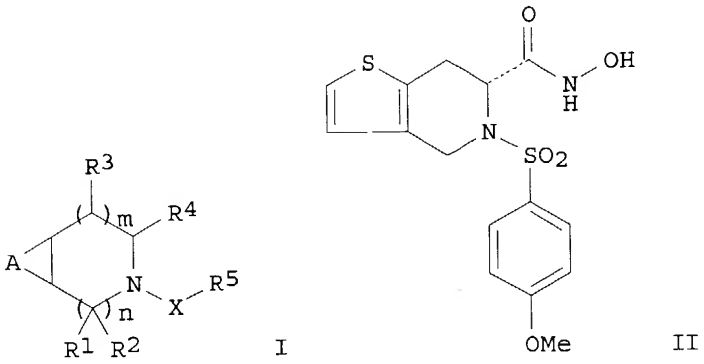
L21 ANSWER 23 OF 28 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:720114 HCAPLUS
DOCUMENT NUMBER: **128:13253**
TITLE: Fused pyridine N-hydroxy carboxamide derivatives and analogs as inhibitors of **metalloproteases**, process for their preparation, and pharmaceutical compositions containing them
INVENTOR(S): De Nanteuil, Guillaume; Paladino, Joseph; Remond, Georges; Atassi, Ghanem; Pierre, Alain; Tucker, Gordon; Bonnet, Jacqueline; Sabatini, Massimo
PATENT ASSIGNEE(S): Adir Et Compagnie, Fr.
SOURCE: Eur. Pat. Appl., 31 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 803505	A1	19971029	EP 1997-400913	19970423
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
FR 2748026	A1	19971031	FR 1996-5321	19960426
FR 2748026	B1	19980605		
NO 9701862	A	19971027	NO 1997-1862	19970423
CA 2203618	AA	19971026	CA 1997-2203618	19970424
CA 2203618	C	20020528		
AU 9719121	A1	19971030	AU 1997-19121	19970424
AU 713680	B2	19991209		
ZA 9703647	A	19971119	ZA 1997-3647	19970425
CN 1165817	A	19971126	CN 1997-109728	19970425

JP 10059936	A2	19980303	JP 1997-108954	19970425
US 5866587	A	19990202	US 1997-842982	19970425
PRIORITY APPLN. INFO.:			FR 1996-5321	A 19960426

OTHER SOURCE(S): CASREACT 128:13253; MARPAT 128:13253

GI



I II

AB Title compds. I are disclosed [wherein m, n = 0, 1, 2; R1, R2 = H, alkyl, aralkyl, aryl; or R1R2 = O, alkylene; R3 = H, alkyl, OH, alkoxy, or aryl; R4 = CONR6OR6', CSNR6OR6', C(:NH)NR6OR6', CO2R7, NHCONHOH, NHCH2CO2R7, CH(NHR7')CO2R7, CH(CO2R7)2; X = SO2, CO, SO2NH; R5 = alkyl (optionally bearing halo, OH, alkoxy, aryl, or CO2R7), cycloalkyl, aryl, or heterocyclyl; R6, R6' = H or alkyl; R7, R7' = H, alkyl, aralkyl; A = fused aromatic (with provisos) or heterocyclic ring]. I are **metalloprotease** inhibitors, potentially useful for treatment of cancer, rheumatoid arthritis, atherosclerosis, etc. Examples include 30 syntheses of I, 19 prophetic compds., 4 biol. screens for selected compds., and a formulation. For instance, (R)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine-6-carboxylic acid hydrochloride underwent a sequence of N-sulfonylation with 4-MeOC6H4SO2Cl, amidation with H2NOCH2CH:CH2.HCl, and Pd-mediated deallylation, to give preferred title compound II. In tests for protection of guinea pig cartilaginous matrix against IL-1β-induced degradation, II gave 98% protection of collagens and 45% protection of proteoglycans.

ED Entered STN: 14 Nov 1997

IC ICM C07D495-04
ICS C07D471-04; C07D221-10; C07D217-26; C07D209-42; C07D493-04; A61K031-435; A61K031-47; A61K031-415; A61K031-40

ICI C07D471-04, C07D221-00, C07D209-00; C07D471-04, C07D221-00, C07D221-00; C07D493-04, C07D307-00, C07D221-00; C07D495-04

CC 28-2 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1, 7

ST **metalloprotease** inhibitor thienopyridine carboline imidazopyridine isoquinoline; hydroxy carboxamide prepn **metalloprotease** inhibitor

IT Antiarteriosclerotics
(antiatherosclerotics; preparation of fused pyridine N-hydroxy carboxamide derivs. and analogs as **metalloprotease** inhibitors)

IT Collagens, biological studies
Proteoglycans, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)
(inhibition of degradation; preparation of fused pyridine N-hydroxy carboxamide

derivs. and analogs as **metalloprotease** inhibitors)

IT Angiogenesis inhibitors
Antiarthritics
Antitumor agents
(preparation of fused pyridine N-hydroxy carboxamide derivs. and analogs as **metalloprotease** inhibitors)

IT 158456-85-0P 191327-27-2P 198957-52-7P 198957-53-8P 198957-54-9P
198957-55-0P 198957-56-1P 198957-57-2P 198957-58-3P 198957-59-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; preparation of fused pyridine N-hydroxy carboxamide derivs. and analogs as **metalloprotease** inhibitors)

IT 191326-89-3P 191326-90-6P 191327-21-6P 198957-24-3P 198957-25-4P
198957-26-5P 198957-27-6P 198957-28-7P 198957-29-8P 198957-30-1P
198957-31-2P 198957-32-3P 198957-33-4P 198957-34-5P 198957-35-6P
198957-36-7P 198957-37-8P 198957-38-9P 198957-39-0P 198957-40-3P
198957-41-4P 198957-42-5P 198957-43-6P 198957-44-7P 198957-45-8P
198957-46-9P 198957-47-0P 198957-48-1P 198957-49-2P 198957-50-5P
198957-51-6P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of fused pyridine N-hydroxy carboxamide derivs. and analogs as **metalloprotease** inhibitors)

IT 9001-12-1, **MMP**-1 79955-99-0, **MMP**-3 81669-70-7,
Metalloprotease 146480-35-5, **MMP** 2 146480-36-6,
MMP 9
RL: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)
(preparation of fused pyridine N-hydroxy carboxamide derivs. and analogs as **metalloprotease** inhibitors)

IT 93-11-8, 2-Naphthalenesulfonic acid chloride 98-68-0,
4-Methoxybenzenesulfonic acid chloride 100-07-2, 4-Methoxybenzoic acid chloride 124-13-0, Octanal 153-94-6, D-Tryptophan 1623-93-4,
4-Phenylbenzenesulfonic acid chloride 42438-90-4 59981-63-4, Spinacine 62561-76-6, β-(2-Thienyl)-D-alanine 72002-54-1 73948-18-2
76985-09-6 78306-92-0 94108-56-2, 4-(Trifluoromethoxy)benzenesulfonic acid chloride 98667-14-2 103733-65-9, (R)-1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid 111139-55-0 198957-60-7
198957-61-8 198957-62-9 198957-63-0 198957-64-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(starting material; preparation of fused pyridine N-hydroxy carboxamide derivs. and analogs as **metalloprotease** inhibitors)

L21 ANSWER 24 OF 28 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:278955 HCAPLUS
DOCUMENT NUMBER: **126:264355**
TITLE: Preparation of N-containing compounds as Fas ligand solubilization inhibitors
INVENTOR(S): Hirano, Takao; Yagita, Hideo; Okumura, Ko; Hirayama, Ryoichi; Yamamoto, Minoru; Ebata, Tomohiko; Ohmoto, Hiroshi; Ikeda, Shoji; Yoshino, Kohichiro
PATENT ASSIGNEE(S): Kanebo, Ltd., Japan
SOURCE: PCT Int. Appl., 123 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9709066	A1	19970313	WO 1996-JP2492	19960904
W: CA, CN, KR, NO, US				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 848957	A1	19980624	EP 1996-929510	19960904
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
JP 09188631	A2	19970722	JP 1996-257868	19960906
PRIORITY APPLN. INFO.:			JP 1995-256897	19950908
			JP 1995-317136	19951109
			WO 1996-JP2492	19960904

OTHER SOURCE(S): MARPAT 126:264355

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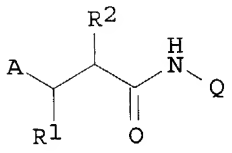

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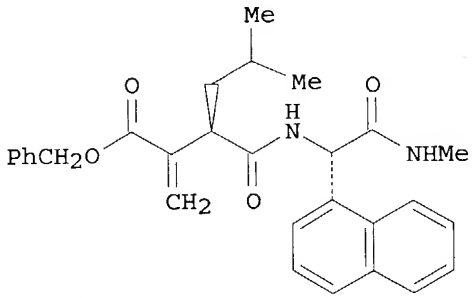
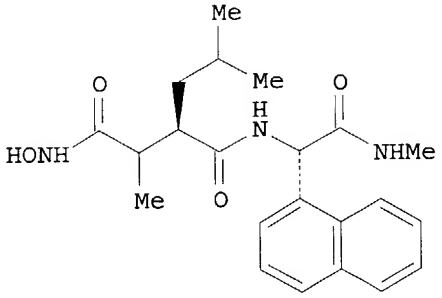


II



III

AB The title compds. (I; A = N-hydroxyaminocarbonyl, CO2H, SH, etc.; R1 = H, NH2, OH, SH, C1-6 alkoxy or alkyl, etc.; R2 = H, C1-6 alkyl or **alkylthio**, C2-6 alkenyl, etc.; R3 = C1-6 alkyl, C2-6 alkenyl, etc.; R4 = H, C1-6 alkyl or alkoxy, etc.; R5 = H, C1-6 alkyl, etc.; R6 = H, OH, C1-6 alkoxy, etc.; R7 = H, OH, OMe; n = 5-7) or pharmaceutically acceptable salts thereof are prepared I, having a matrix **metalloprotease** inhibitory activity, are useful as Fas ligand solubilization inhibitors in the prevention or treatment of diseases caused by solubilized Fas ligands such as hepatitis, GVHD, AIDS, and autoimmune diseases. Thus, L-alanine derivative (II) was hydrogenated over Pd/C, reacted with C6H4CH2ONH2.HCl in the presence of WSC, Et3N, and hydroxybenzotriazole, and then hydrogenated again over Pd/C to give the title compound (III). III showed 50% Fas ligand secretion inhibitory when tested on mouse p.o.

ED Entered STN: 01 May 1997

IC ICM A61K045-00
ICS A61K031-165; A61K031-47; A61K031-55; C07D487-04; C07C239-18

CC 34-2 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1, 28, 63

ST Fas ligand solubilization inhibitor nitrogen compd; matrix **metalloprotease** inhibitor nitrogen compd; hepatitis treatment nitrogen compd prepn; GVHD treatment nitrogen compd prepn; AIDS treatment nitrogen compd prepn; autoimmune disease treatment nitrogen compd prepn

IT 81669-70-7, **Metalloprotease**
RL: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)
(matrix; preparation of N-containing compds. as Fas ligand solubilization inhibitors)

IT 50-00-0, Formaldehyde, reactions 66-99-9, 2-Naphthaldehyde 74-89-5, Methylamine, reactions 91-21-4, 1,2,3,4-Tetrahydroisoquinoline 100-39-0, Benzyl bromide 108-18-9, Diisopropylamine 108-98-5, **Thiophenol**, reactions 110-91-8, Morpholine, reactions 501-53-1, Benzyloxycarbonyl chloride 541-41-3, Ethyl chlorocarbonate 1821-12-1, 4-Phenylbutyric acid 2270-20-4, 5-Phenylpentanoic acid 2687-43-6, O-Benzylhydroxylamine hydrochloride 5292-43-3, tert-Butyl bromoacetate 18496-54-3, 4-Phenylbutanoyl chloride 41153-30-4 55447-00-2 56613-80-0 100564-78-1 129213-83-8 133899-27-1 145963-04-8 155947-71-0 162117-96-6 168158-22-3 170450-78-9 188729-11-5 188729-12-6
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of N-containing compds. as Fas ligand solubilization inhibitors)

L21 ANSWER 25 OF 28 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1996:731972 HCAPLUS
DOCUMENT NUMBER: **126:8011**
TITLE: Preparation of 3-[(hydroxaminocarbonyl)alkanamido]caprolactams and analogs as matrix **metalloprotease** inhibitors
INVENTOR(S): De, Biswanath; Cheng, Menyen; Natchus, Michael George; Wahl, Christopher Thomas
PATENT ASSIGNEE(S): Procter and Gamble Company, USA
SOURCE: PCT Int. Appl., 60 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9629313	A1	19960926	WO 1996-US3726	19960319
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML				
US 5672598	A	19970930	US 1995-407839	19950321
IL 117527	A1	19991222	IL 1996-117527	19960318
CA 2216129	AA	19960926	CA 1996-2216129	19960319
CA 2216129	C	20020820		
AU 9652558	A1	19961008	AU 1996-52558	19960319
AU 711889	B2	19991021		
EP 815084	A1	19980107	EP 1996-908856	19960319
EP 815084	B1	20030827		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
CN 1179151	A	19980415	CN 1996-192669	19960319
BR 9607772	A	19980707	BR 1996-7772	19960319

JP 11502523	T2	19990302	JP 1996-528560		19960319
AT 248150	E	20030915	AT 1996-908856		19960319
ZA 9602253	A	19960930	ZA 1996-2253		19960320
NO 9704335	A	19971121	NO 1997-4335		19970919
PRIORITY APPLN. INFO.:			US 1995-407839	A	19950321
			WO 1996-US3726	W	19960319

OTHER SOURCE(S): MARPAT 126:8011

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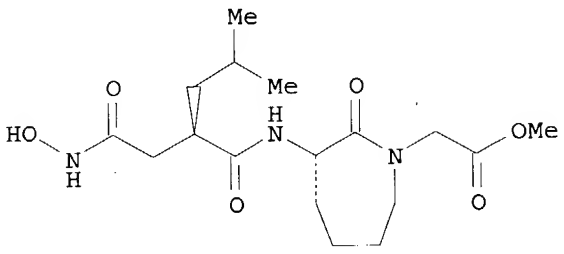


I

AB HONHCOCHR1CHR2CONR3CHR8CONR4R9 [R1 = H, alkyl, alkoxy, heterocyclyl, etc.; R2 = H, OH, alkyl, heterocyclyl, etc.; R1R2 = alkylene; R3 = H or (cyclo)alkyl; R4 = (cyclo)alkyl, alkoxycarbonyl(alkyl), arylsulfonyl, etc.; R8R9 = (CR2)n, CH:CH, etc.; n = 2-4] were prepared as matrix **metalloprotease** inhibitors (no data). Thus, (S)-caprolactam-3-amine was amidated by (R)-Me3CO2CCH2CH(CH2CHMe2)CO2H and the product N-alkylated by BrCH2CO2Me to give, in 2 addnl. steps, title compound I.

ED Entered STN: 13 Dec 1996

IC ICM C07D223-12
ICS C07D211-76; C07D213-75; A61K031-55; A61K031-445; A61K031-44

CC 27-21 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 1

ST alkanamidocaprolactam hydroxaminocarbonyl prepn matrix **metalloprotease** inhibitor

IT 81669-70-7, Metalloproteinase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(matrix; mediated diseases; treatment; preparation of 3-[(hydroxaminocarbonyl)alkanamido]caprolactams and analogs as matrix **metalloprotease** inhibitors)

IT 183665-06-7P 183665-08-9P 183665-09-0P 183665-10-3P 183665-12-5P
183665-14-7P 183665-15-8P 183665-17-0P 183665-18-1P 183665-19-2P
183665-20-5P 183665-21-6P 183665-22-7P 183665-23-8P 183665-26-1P
183665-29-4P 183665-33-0P 183665-34-1P 183665-35-2P 183901-48-6P
183901-49-7P 183901-50-0P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of 3-[(hydroxaminocarbonyl)alkanamido]caprolactams and analogs as matrix **metalloprotease** inhibitors)

IT 96-32-2, Methyl bromoacetate 98-59-9, Tosyl chloride 100-39-0, Benzyl bromide 100-46-9, Benzylamine, reactions 109-65-9, 1-Bromobutane 109-73-9, Butylamine, reactions 112-13-0, Decanoyl chloride 622-33-3, O-Benzyl hydroxylamine 2528-61-2, Heptanoyl chloride 3184-13-2, L-Ornithine hydrochloride 5292-43-3, tert-Butyl bromoacetate 5437-45-6, Benzylbromoacetate 6332-56-5, 2-Hydroxy-3-nitropyridine 6482-24-2, 2-BrOmoethyl methyl ether 21568-87-6, (S)-Caprolactam-3-amine 24424-99-5, Di-tert-butyl dicarbonate 90719-32-7, (S)-4-Benzyl-2-

oxazolidinone 112245-04-2 135775-09-6 148415-74-1 148415-75-2
148415-76-3
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of 3-[(hydroxaminocarbonyl)alkanamido]caprolactams and analogs as matrix **metalloprotease** inhibitors)

IT 34294-79-6P 76944-95-1P 82611-52-7P 92235-39-7P 93961-02-5P
93961-04-7P 153427-69-1P 153427-89-5P 175210-67-0P 183665-36-3P
183665-37-4P 183665-38-5P 183665-39-6P 183665-40-9P 183665-41-0P
183665-42-1P 183665-43-2P 183665-44-3P 183665-45-4P 183665-46-5P
183665-47-6P 183665-48-7P 183665-49-8P 183665-50-1P 183665-51-2P
183665-52-3P 183665-53-4P 183665-54-5P 183665-55-6P 183665-56-7P
183665-57-8P 183665-58-9P 183665-59-0P 183665-60-3P 183665-61-4P
183665-62-5P 183665-63-6P 183665-64-7P 183665-65-8P 183665-66-9P
183665-67-0P 183665-68-1P 183665-70-5P 183665-71-6P 183665-73-8P
183665-76-1P 183665-78-3P 183665-81-8P 183665-83-0P 183665-85-2P
183665-87-4P 183665-88-5P 183665-89-6P 183665-90-9P 183665-91-0P
183665-92-1P 183665-93-2P 183665-94-3P 183665-95-4P 183665-96-5P
183665-97-6P 183665-98-7P 183665-99-8P 183666-00-4P 183666-01-5P
183666-02-6P 183666-03-7P 183666-04-8P 183666-05-9P 183666-06-0P
183666-07-1P 183666-08-2P 183666-09-3P 183666-10-6P 183666-11-7P
183666-12-8P 183901-51-1P 183901-52-2P 183901-53-3P 183901-54-4P
183901-55-5P 183901-56-6P 183901-57-7P 183901-58-8P 183901-59-9P
183901-60-2P 183901-61-3P 183901-62-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of 3-[(hydroxaminocarbonyl)alkanamido]caprolactams and analogs as matrix **metalloprotease** inhibitors)

L21 ANSWER 26 OF 28 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1996:546363 HCAPLUS
DOCUMENT NUMBER: **125:189378**
TITLE: Hydroxamic acid-containing inhibitors of matrix **metalloproteases** and their use in pharmaceuticals
INVENTOR(S): Yelm, Kenneth Edward
PATENT ASSIGNEE(S): Procter and Gamble Company, USA
SOURCE: PCT Int. Appl., 45 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9620918	A1	19960711	WO 1995-US16140	19951213
W: AL, AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5639746	A	19970617	US 1994-366062	19941229
CA 2208679	AA	19960711	CA 1995-2208679	19951213
AU 9644220	A1	19960724	AU 1996-44220	19951213
AU 706409	B2	19990617		
BR 9510175	A	19971014	BR 1995-10175	19951213
EP 800510	A1	19971015	EP 1995-943083	19951213
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE				

CN 1171780	A	19980128	CN 1995-197203	19951213
JP 10512241	T2	19981124	JP 1995-521011	19951213
NO 9703035	A	19970829	NO 1997-3035	19970627
PRIORITY APPLN. INFO.:			US 1994-366062	19941229
			WO 1995-US16140	19951213

OTHER SOURCE(S): MARPAT 125:189378

AB The invention provides hydroxamic acid-containing compds. which are useful as inhibitors of matrix **metalloproteases** and which are effective in treating conditions associated with excess activity of these enzymes. In particular, the present invention relates to a compound having structure HONHCOCHR1NR2COCHR3CHR4COR5 (R1-5 are independently selected from various substituents; or R3 and R4 or R4 and R5 may together comprise a cyclic moiety) or a pharmaceutically-acceptable salt, biohydrolyzable amide or biohydrolyzable ester thereof. In other aspects, the invention is directed to pharmaceutical compns. containing the above compds. and to methods of treating diseases characterized by matrix **metalloprotease** activity using these compds. or the pharmaceutical compns. containing them. Eight of the hydroxamic acid containing inhibitors were synthesized.

ED Entered STN: 13 Sep 1996

IC ICM C07C259-06
ICS A61K031-16

CC 7-3 (Enzymes)
Section cross-reference(s): 21, 63

IT 141907-41-7, Matrix metalloproteinase
RL: MSC (Miscellaneous)
(hydroxamic acid-containing inhibitors of matrix **metalloproteases** and their use in pharmaceuticals)

IT 64-04-0, Phenethylamine 78-81-9, Isobutylamine 112-31-2, Decyl aldehyde 122-78-1, Phenylacetaldehyde 598-21-0, Bromoacetyl bromide 646-07-1, 4-Methylvaleric acid 1438-96-6 2016-57-1, Decylamine 2687-43-6, O-Benzylhydroxylamine hydrochloride 5241-58-7 5292-43-3 7764-95-6 14166-21-3, trans-1,2-Cyclohexanedicarboxylic anhydride 82732-07-8 90719-32-7, (S)-4-Benzyl-2-oxazolidinone
RL: RCT (Reactant); RACT (Reactant or reagent)
(hydroxamic acid-containing inhibitors of matrix **metalloproteases** and their use in pharmaceuticals)

IT 38136-29-7P, 4-Methylvaleroyl chloride 78158-32-4P 112245-04-2P 113543-30-9P 144287-83-2P 180711-88-0P 180711-89-1P 180711-90-4P 180711-91-5P 180711-93-7P 180711-94-8P 180711-96-0P 180711-97-1P 180711-98-2P 180712-00-9P 180712-01-0P 180712-02-1P 180712-04-3P 180712-05-4P 180712-07-6P 180712-08-7P 180712-09-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(hydroxamic acid-containing inhibitors of matrix **metalloproteases** and their use in pharmaceuticals)

IT 180711-92-6P 180711-95-9P 180711-99-3P 180712-03-2P 180712-06-5P 180712-10-1P 180978-86-3P 180978-87-4P
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(hydroxamic acid-containing inhibitors of matrix **metalloproteases** and their use in pharmaceuticals)

L21 ANSWER 27 OF 28 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER:	1994:95761 HCAPLUS
DOCUMENT NUMBER:	**120:95761**
TITLE:	Use of matrix **metalloprotease** (**MMP**) inhibitors as antitumor agents
INVENTOR(S):	Brown, Peter Duncan; Bawden, Lindsay Jayne; Miller, Karen Margrete
PATENT ASSIGNEE(S):	British Bio-Technology Ltd., UK

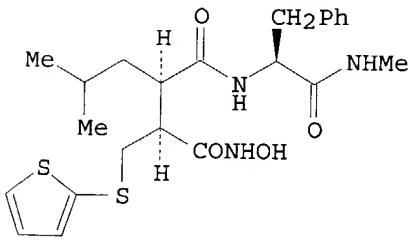
SOURCE: PCT Int. Appl., 48 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9321942	A2	19931111	WO 1993-GB888	19930429
WO 9321942	A3	19940120		
W: AU, BR, CA, CZ, FI, HU, JP, KR, NO, NZ, PL, PT, RU, SK, UA, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9342672	A1	19931129	AU 1993-42672	19930429
EP 1002556	A2	20000524	EP 1999-114903	19930429
EP 1002556	A3	20010110		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE				
ZA 9303089	A	19931123	ZA 1993-3089	19930430
US 5872152	A	19990216	US 1996-686485	19960726

PRIORITY APPLN. INFO.:

GB 1992-9513	A	19920501
GB 1993-5817	A	19930320
EP 1993-911883	A3	19930429
WO 1993-GB888	A	19930429
US 1993-133081	B1	19931202

OTHER SOURCE(S): MARPAT 120:95761
GI



I

AB Various known hydroxamic acid **MMPs** are useful in the preparation of agents for promoting tumor regression and/or inhibiting cancer cell proliferation. Thus, I inhibited proliferation of human melanoma cells in vitro at 3 μM, and markedly increased the survival time of mice bearing a human ovarian carcinoma xenograft when administered at 40 mg/kg/day i.p.

ED Entered STN: 05 Mar 1994

IC ICM A61K037-02

CC 1-6 (Pharmacology)

IT Psoriasis
(angiogenesis inhibition in, with matrix **metalloprotease** inhibitors)

IT Blood vessel
(formation of, matrix **metalloprotease** inhibitors effect on, neoplasm inhibition in relation to)

IT Neoplasm inhibitors
(matrix **metalloprotease**-inhibiting hydroxamates)

IT Hydroxamic acids
RL: BIOL (Biological study)
(matrix **metalloprotease**-inhibiting, neoplasm inhibition by)

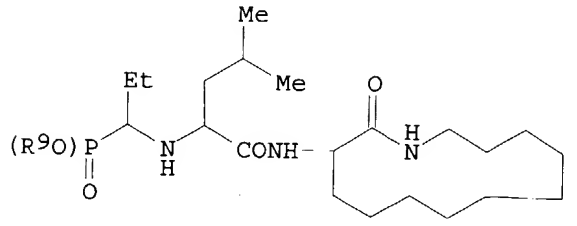
IT Diabetes mellitus
(retinopathy in, angiogenesis inhibition in, with matrix **metalloprotease** inhibitors)
IT Neoplasm inhibitors
(carcinoma, matrix **metalloprotease**-inhibiting hydroxamates)
IT Kidney, neoplasm
Lung, neoplasm
Ovary, neoplasm
Pancreas, neoplasm
Stomach, neoplasm
(carcinoma, inhibitors, matrix **metalloprotease**-inhibiting hydroxamates)
IT Uterus, neoplasm
(cervix, carcinoma, inhibitors, matrix **metalloprotease**-inhibiting hydroxamates)
IT Neoplasm inhibitors
(colon carcinoma, matrix **metalloprotease**-inhibiting hydroxamates)
IT Intestine, neoplasm
(colon, carcinoma, inhibitors, matrix **metalloprotease**-inhibiting hydroxamates)
IT Neoplasm inhibitors
(kidney carcinoma, matrix **metalloprotease**-inhibiting hydroxamates)
IT Neoplasm inhibitors
(lung carcinoma, matrix **metalloprotease**-inhibiting hydroxamates)
IT Neoplasm inhibitors
(mammary gland carcinoma, matrix **metalloprotease**-inhibiting hydroxamates)
IT Neoplasm inhibitors
(melanoma, matrix **metalloprotease**-inhibiting hydroxamates)
IT Neoplasm inhibitors
(metastasis, matrix **metalloprotease**-inhibiting hydroxamates)
IT Mammary gland
Prostate gland
(neoplasm, carcinoma, inhibitors, matrix **metalloprotease**-inhibiting hydroxamates)
IT Neoplasm inhibitors
(neuroectoderm, matrix **metalloprotease**-inhibiting hydroxamates)
IT Nervous system
(neuroectoderm, neoplasm, inhibitors, matrix **metalloprotease**-inhibiting hydroxamates)
IT Neoplasm inhibitors
(ovary carcinoma, matrix **metalloprotease**-inhibiting hydroxamates)
IT Neoplasm inhibitors
(pancreas carcinoma, matrix **metalloprotease**-inhibiting hydroxamates)
IT Neoplasm inhibitors
(prostate gland carcinoma, matrix **metalloprotease**-inhibiting hydroxamates)
IT Eye, disease
(pterygium, angiogenesis inhibition in, with matrix **metalloprotease** inhibitors)
IT Neoplasm inhibitors
(rectum carcinoma, matrix **metalloprotease**-inhibiting hydroxamates)
IT Intestine, neoplasm

(rectum, carcinoma, inhibitors, matrix **metalloprotease** -inhibiting hydroxamates)
IT Eye, disease
(retinopathy, in diabetes mellitus, angiogenesis inhibition in, with matrix **metalloprotease** inhibitors)
IT Neoplasm inhibitors
(sarcoma, matrix **metalloprotease**-inhibiting hydroxamates)
IT Neoplasm inhibitors
(stomach carcinoma, matrix **metalloprotease**-inhibiting hydroxamates)
IT Neoplasm inhibitors
(uterus cervix carcinoma, matrix **metalloprotease**-inhibiting hydroxamates)

L21 ANSWER 28 OF 28 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1991:229399 HCAPLUS
DOCUMENT NUMBER: **114:229399**
TITLE: Preparation of phosphonoalkylpeptides with collagenase inhibiting activity
INVENTOR(S): Markwell, Roger Edward; Ward, Robert William; Hunter, David James
PATENT ASSIGNEE(S): Beecham Group PLC, UK
SOURCE: Eur. Pat. Appl., 29 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 401963	A1	19901212	EP 1990-303851	19900410
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
CA 2014375	AA	19901013	CA 1990-2014375	19900411
AU 9053158	A1	19901018	AU 1990-53158	19900411
AU 618669	B2	19920102		
ZA 9002775	A	19910626	ZA 1990-2775	19900411
JP 03063294	A2	19910319	JP 1990-96589	19900413
US 5212163	A	19930518	US 1991-758356	19910909
PRIORITY APPLN. INFO.:			GB 1989-8353 A	19890413
			GB 1989-17756 A	19890803
			US 1990-508272 B1	19900411

OTHER SOURCE(S): MARPAT 114:229399
GI



II

AB HO(RO)P(O)CHR1NHCHR2CONHCHR3CONHR4 [I; R = H, C1-6 alkyl, (substituted) PhCH2; R1 = H, C1-6 alkyl; R2 = C3-6 alkyl; R3 = H, alkyl, CH2Z, CHR8OR7; Z = (substituted) Ph or heteroaryl; R7 = H, alkyl, (substituted) PhCH2; R8

= H, alkyl; R4 = CH2(CH2)nOR5, CH2(CH2)nO2CR6; n = 1-6; R5, R6 = H, C1-6 alkyl; or R3R4 = (CH2)m; m = 4-12], useful as inhibitors of neutral **metalloproteases** for treatment of arthritic diseases, bone resorption diseases, degradation of connective tissue, etc., are prepared

Thus, condensation of N-[(S)-1-diethoxyphosphinylpropyl]-(R or S)-leucine with (-)-3-aminoazacyclotridecan-2-one in the presence of 1-hydroxybenzotriazole and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide-HCl in CH2Cl2 and deprotection of the resulting amide (II; R9 = Et) with Me3SiBr in CH2Cl2 gave II (R9 = H) (III). (S,S)-III in vitro showed IC50 = 0.045 μM against human lung fibroblast collagenase.

ED Entered STN: 15 Jun 1991

IC ICM C07K005-06
ICS C07F009-38; A61K037-64; A61K031-66

CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1, 7

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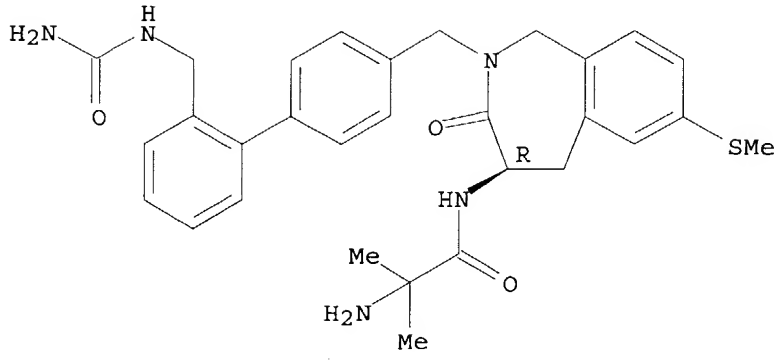
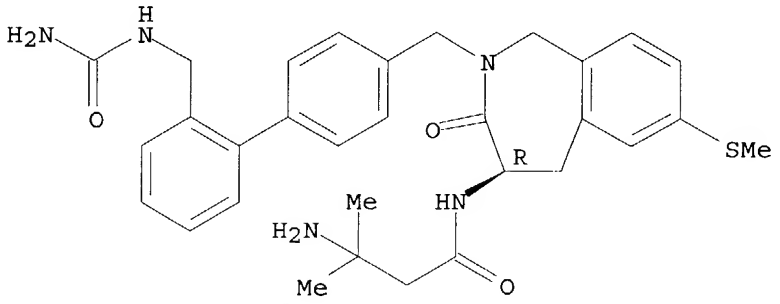


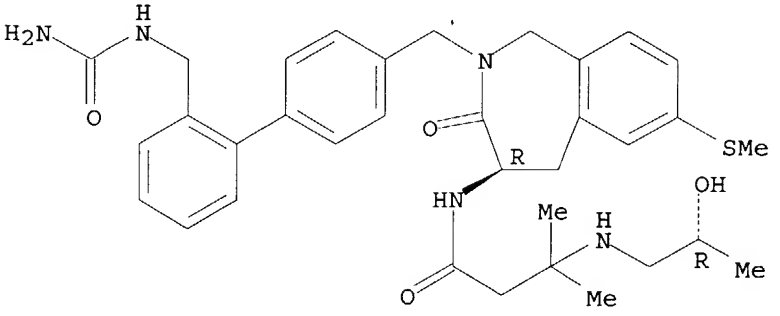
RN 168057-69-0 HCAPLUS
CN Butanamide, 3-amino-N-[2-[[2'-[[(aminocarbonyl)amino]methyl][1,1'-biphenyl]-4-yl]methyl]-2,3,4,5-tetrahydro-7-(methylthio)-3-oxo-1H-2-benzazepin-4-yl]-3-methyl-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



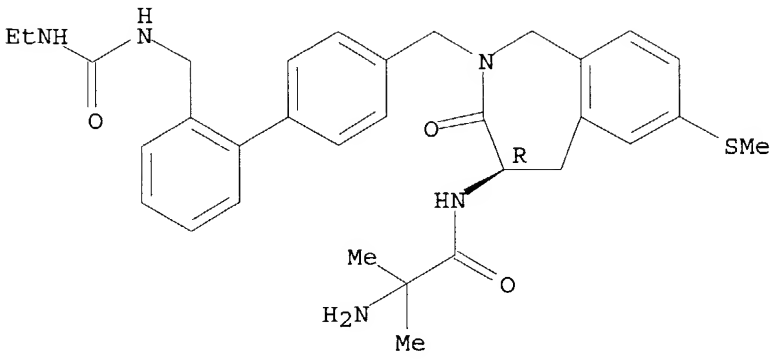
RN 168057-72-5 HCAPLUS
CN Butanamide, N-[2-[[2'-[[(aminocarbonyl)amino]methyl][1,1'-biphenyl]-4-yl]methyl]-2,3,4,5-tetrahydro-7-(methylthio)-3-oxo-1H-2-benzazepin-4-yl]-3-[(2-hydroxypropyl)amino]-3-methyl-, [R-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



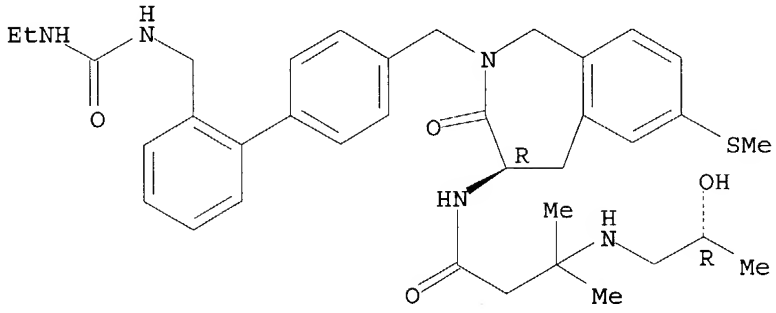
RN 168057-78-1 HCAPLUS
CN Propanamide, 2-amino-N-[2-[[2'-[[[(ethylamino)carbonyl]amino]methyl][1,1'-biphenyl]-4-yl]methyl]-2,3,4,5-tetrahydro-7-(methylthio)-3-oxo-1H-2-benzazepin-4-yl]-2-methyl-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



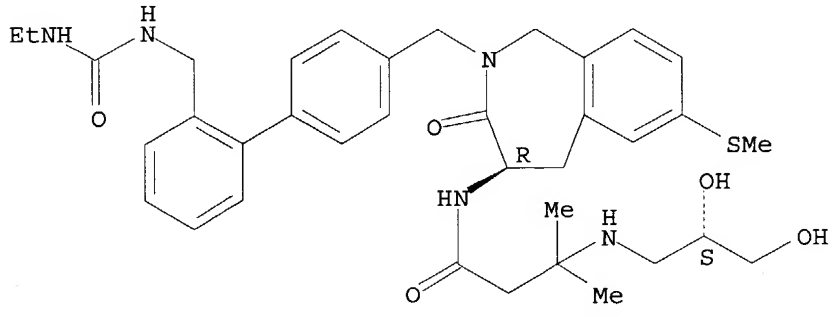
RN 168057-84-9 HCAPLUS
CN Butanamide, N-[2-[[2'-[[[(ethylamino)carbonyl]amino]methyl][1,1'-biphenyl]-4-yl]methyl]-2,3,4,5-tetrahydro-7-(methylthio)-3-oxo-1H-2-benzazepin-4-yl]-3-[(2-hydroxypropyl)amino]-3-methyl-, [R-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 168057-88-3 HCAPLUS
CN Butanamide, 3-[(2,3-dihydroxypropyl)amino]-N-[2-[[2'-[[[(ethylamino)carbonyl]amino]methyl][1,1'-biphenyl]-4-yl]methyl]-2,3,4,5-tetrahydro-7-(methylthio)-3-oxo-1H-2-benzazepin-4-yl]-3-methyl-, [S-(R*,S*)]- (9CI) (CA INDEX NAME)

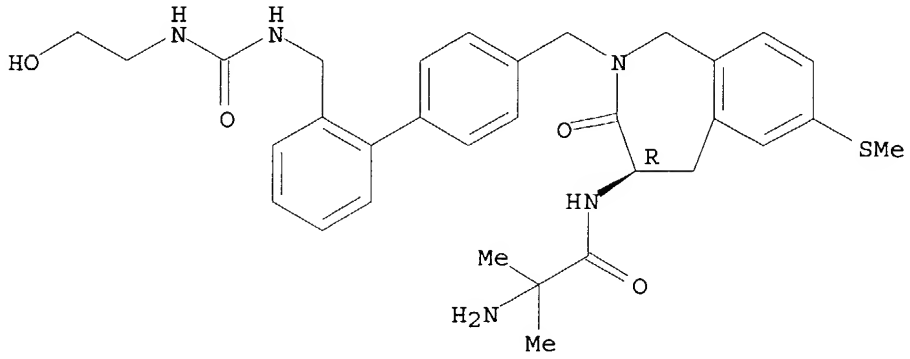
Absolute stereochemistry.



RN 168057-92-9 HCAPLUS

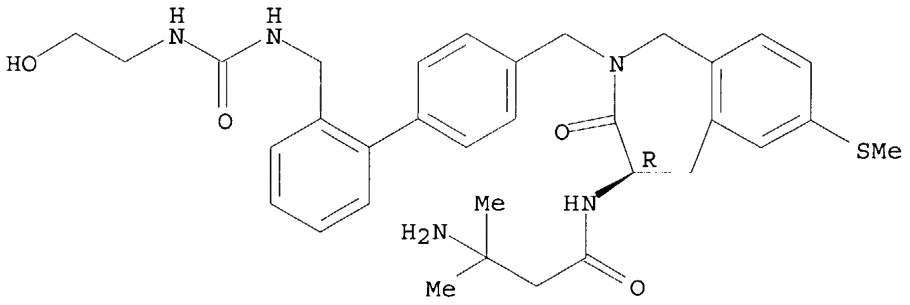
CN Propanamide, 2-amino-2-methyl-N-[2,3,4,5-tetrahydro-2-[[2'-[[[[(2-hydroxyethyl)amino]carbonyl]amino]methyl][1,1'-biphenyl]-4-yl]methyl]-7-(methylthio)-3-oxo-1H-2-benzazepin-4-yl]-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



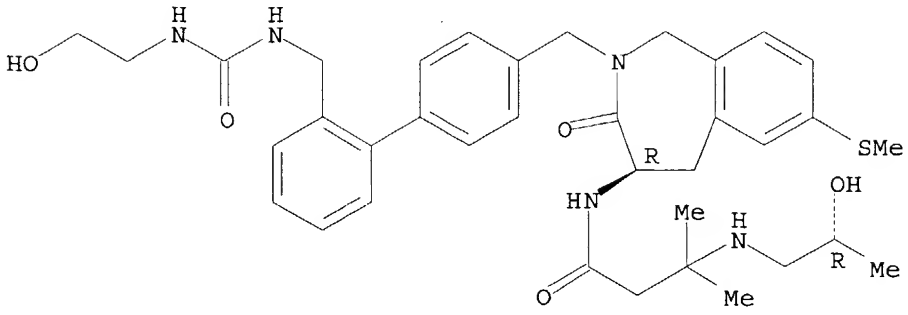
RN 168057-96-3 HCAPLUS
CN Butanamide, 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-[[2'-[[[[(2-hydroxyethyl)amino]carbonyl]amino]methyl][1,1'-biphenyl]-4-yl]methyl]-7-(methylthio)-3-oxo-1H-2-benzazepin-4-yl]-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



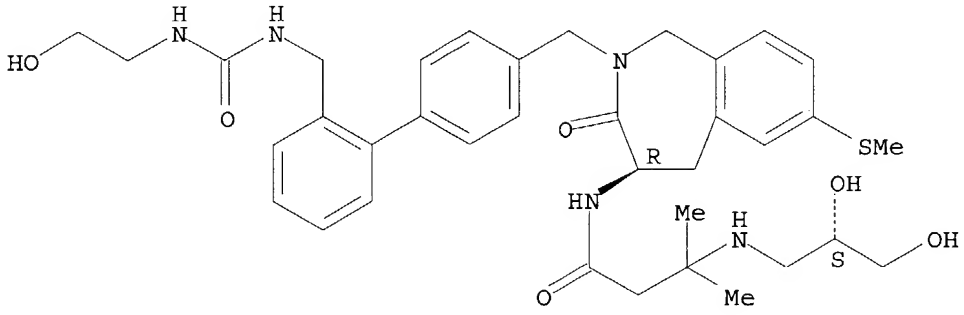
RN 168058-00-2 HCAPLUS
CN Butanamide, 3-[(2-hydroxypropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-[[2'-[[[[(2-hydroxyethyl)amino]carbonyl]amino]methyl][1,1'-biphenyl]-4-yl]methyl]-7-(methylthio)-3-oxo-1H-2-benzazepin-4-yl]-, [R-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 168058-04-6 HCAPLUS
CN Butanamide, 3-[(2,3-dihydroxypropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-[[2'-[[[[(2-hydroxyethyl)amino]carbonyl]amino]methyl][1,1'-biphenyl]-4-yl]methyl]-7-(methylthio)-3-oxo-1H-2-benzazepin-4-yl]-, [R-(R*,S*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L52 ANSWER 11 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1995:867574 HCAPLUS
DOCUMENT NUMBER: 123:256544
ENTRY DATE: Entered STN: 20 Oct 1995
TITLE: Preparation of N-(oxobenzazepinyl)alkanamides as growth hormone release promoters
INVENTOR(S): Schoen, William R.; Wyvratt, Matthew J., Jr.; Hodges, Paul J.
PATENT ASSIGNEE(S): Merck and Co., Inc., USA
SOURCE: PCT Int. Appl., 134 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
INT. PATENT CLASSIF.:
MAIN: C07D281-10
SECONDARY: C07D223-16; C07D281-18; C07D223-06; A61K031-55
CLASSIFICATION: 27-21 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 1
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9503290	A1	19950202	WO 1994-US8228	19940720

W: AU, BB, BG, BR, BY, CA, CN, CZ, FI, GE, HU, JP, KE, KG, KR, KZ, LK, LT, LV, MD, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SI, SK, TJ, TT, UA, US, UZ
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

US 5430144	A	19950704	US 1993-97146	19930726
CA 2167507	AA	19950202	CA 1994-2167507	19940720
AU 9474024	A1	19950220	AU 1994-74024	19940720
AU 683081	B2	19971030		
EP 711287	A1	19960515	EP 1995-906200	19940720
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
JP 09502961	T2	19970325	JP 1994-505304	19940720
ZA 9405462	A	19950303	ZA 1994-5462	19940725
PRIORITY APPLN. INFO.:			US 1993-97146 A	19930726
			WO 1994-US8228 W	19940720

PATENT CLASSIFICATION CODES:

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 9503290	ICM	C07D281-10
	ICS	C07D223-16; C07D281-18; C07D223-06; A61K031-55
US 5430144	ECLA	C07D403/14; C07D405/12; C07D405/14; C07D417/14

OTHER SOURCE(S): CASREACT 123:256544; MARPAT 123:256544
GRAPHIC IMAGE: For diagram(s), see printed CA Issue.
ABSTRACT:
Title compds. [I; A = (CH2)xCR8R80(CH2)y; R = (CH2)qZwR20; R1,R2 = H, halo, alkyl, Ph, etc.; R4 = furfuryl, azolyl(alkyl), etc.; R5 = H, alkyl, Ph, etc.; R6 = H, alkyl, phenyl(alkyl); R8,R80 = H, alkyl, Ph, etc.; R20 = (un)substituted Ph; Z = (un)substituted phenylene; n,w = 0 or 1; p,x,y = 0-3; q = 0-4] were prepared as growth hormone release promoters (no data). Thus, title compound II (R4 = H) was reductively condensed with furfuraldehyde to give II (R4 = furfuryl).

SUPPL. TERM: oxobenzazepinylalkanamide prepn growth hormone release promoter

INDEX TERM: Antiobesity agents
(preparation of N-(oxobenzazepinyl)alkanamides as growth hormone release promoters)

INDEX TERM: Osteoporosis
(treatment; preparation of N-(oxobenzazepinyl)alkanamides as growth hormone release promoters)

INDEX TERM: Animal metabolism
(disorder, catabolic, nitrogen wasting; treatment; preparation of N-(oxobenzazepinyl)alkanamides as growth hormone release promoters)

INDEX TERM:

169187-15-9P	169187-16-0P	169187-18-2P	169187-20-6P
169187-21-7P	169187-22-8P	169187-23-9P	169187-24-0P
169187-25-1P	169187-26-2P	169187-27-3P	169187-28-4P
169187-29-5P	169187-30-8P	169187-31-9P	169187-32-0P
169187-33-1P	169187-34-2P	169187-35-3P	
169187-36-4P	169187-37-5P	169187-38-6P	
169187-39-7P	169187-40-0P	**169187-41-1P**	
169187-42-2P	169187-43-3P	169187-44-4P	169187-45-5P
169187-46-6P	169187-47-7P	169187-48-8P	
169187-49-9P	169187-50-2P	**169187-51-3P**	
169187-52-4P	169187-53-5P	169187-54-6P	169187-55-7P
169187-56-8P	169187-57-9P	169187-58-0P	
169187-59-1P	169187-60-4P	**169187-61-5P**	
169187-62-6P	169187-63-7P	169187-64-8P	169187-65-9P
169187-66-0P	169187-67-1P	169187-68-2P	
169187-69-3P	169187-70-6P	169187-71-7P	169187-72-8P

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169188-09-4P 169188-10-7P 169188-11-8P 169188-12-9P
169188-13-0P 169188-14-1P 169188-15-2P 169188-16-3P
ROLE: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of N-(oxobenzazepinyl)alkanamides as growth hormone release promoters)

INDEX TERM: 169188-17-4P
ROLE: BYP (Byproduct); PREP (Preparation)
(preparation of N-(oxobenzazepinyl)alkanamides as growth hormone release promoters)

INDEX TERM: 98-01-1, Furfuraldehyde, reactions 110-87-2 577-19-5, 2-Bromo-1-nitrobenzene 620-02-0, 5-Methylfuran-2-carboxaldehyde 5720-05-8, 4-Tolylboronic acid 10111-08-7, 2-Imidazolecarboxaldehyde 145485-77-4 169188-19-6
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(preparation of N-(oxobenzazepinyl)alkanamides as growth hormone release promoters)

INDEX TERM: 70680-21-6P 114772-39-3P 145457-11-0P 159814-82-1P
159814-84-3P 159815-76-6P 159815-77-7P 159815-78-8P
159815-79-9P 159815-80-2P 159815-81-3P 159815-82-4P
159815-83-5P 169188-18-5P
ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of N-(oxobenzazepinyl)alkanamides as growth hormone release promoters)

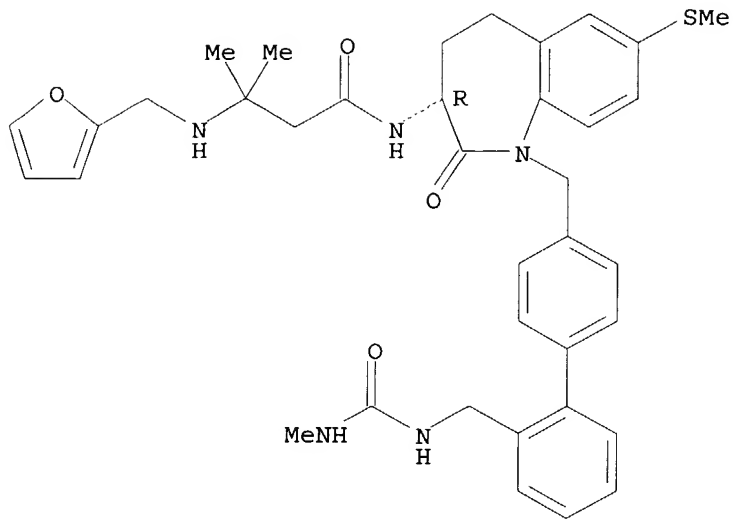
INDEX TERM: 12629-01-5, Human growth hormone
ROLE: BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study)
(release; preparation of N-(oxobenzazepinyl)alkanamides as growth hormone release promoters)

IT **169187-36-4P 169187-41-1P 169187-46-6P**
169187-51-3P 169187-56-8P 169187-61-5P
169187-66-0P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of N-(oxobenzazepinyl)alkanamides as growth hormone release promoters)

RN 169187-36-4 HCAPLUS

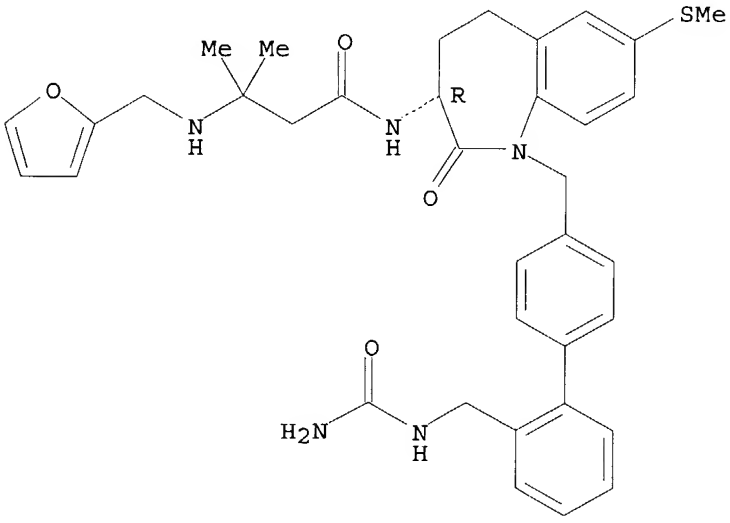
CN Butanamide, 3-[(2-furanylmethyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-1-[[2'-[[[(methylamino)carbonyl]amino]methyl][1,1'-biphenyl]-4-yl]methyl]-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



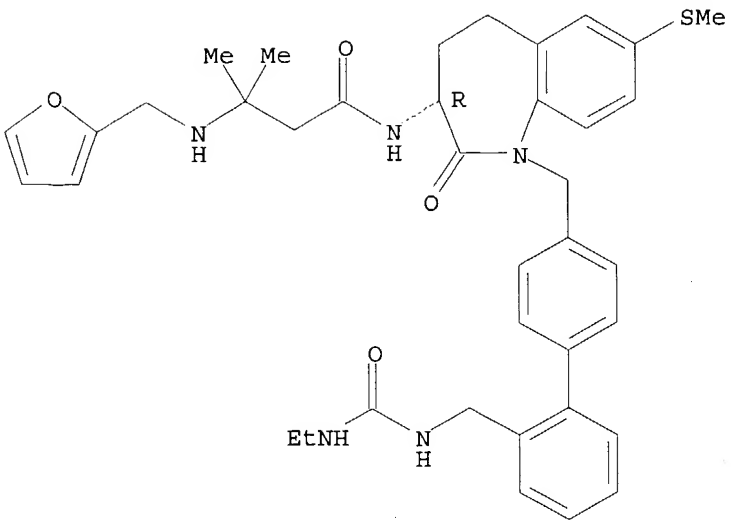
RN 169187-41-1 HCAPLUS
CN Butanamide, N-[1-[[2'-[[(aminocarbonyl)amino]methyl][1,1'-biphenyl]-4-yl]methyl]-2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-3-[(2-furanylmethyl)amino]-3-methyl-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



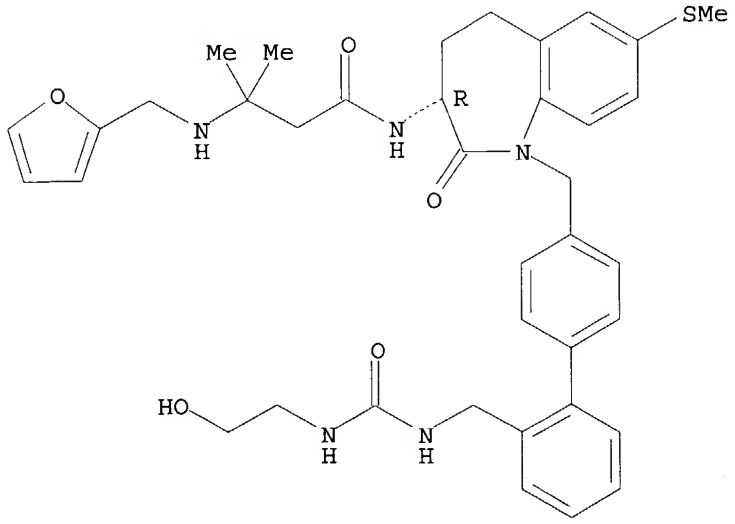
RN 169187-46-6 HCAPLUS
CN Butanamide, N-[1-[[2'-[[[(ethylamino)carbonyl]amino]methyl][1,1'-biphenyl]-4-yl]methyl]-2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-3-[(2-furanylmethyl)amino]-3-methyl-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



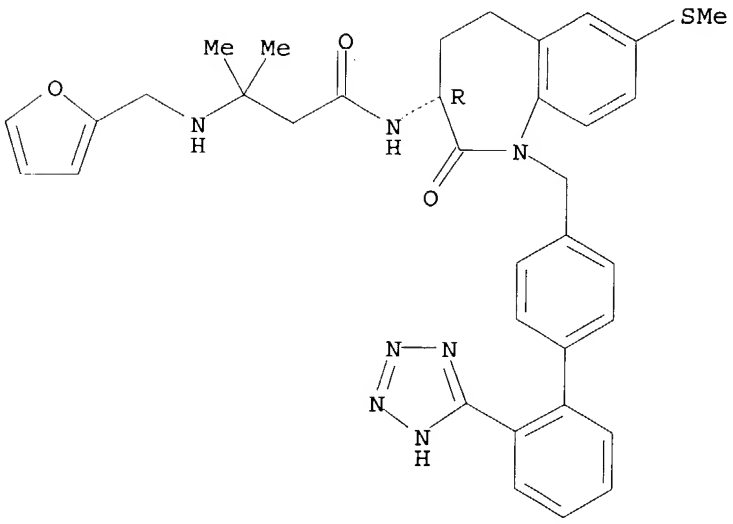
RN 169187-51-3 HCAPLUS
CN Butanamide, 3-[(2-furanylmethyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-1-[[2'-[[[[(2-hydroxyethyl)amino]carbonyl]amino]methyl][1,1'-biphenyl]-4-yl]methyl]-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



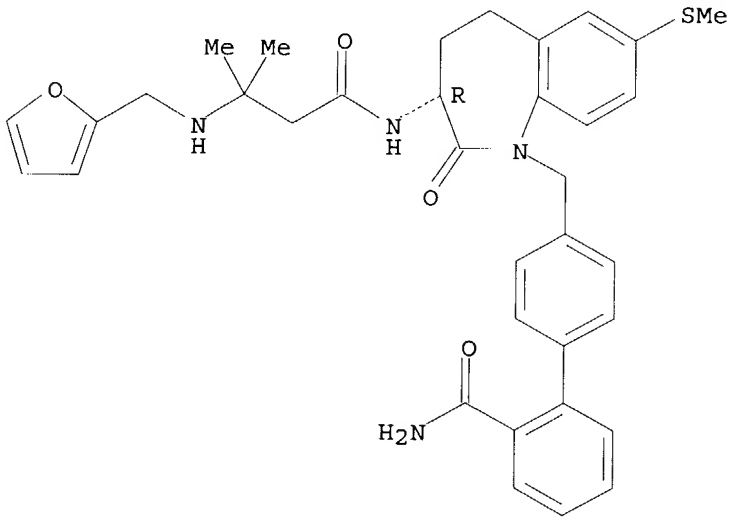
RN 169187-56-8 HCAPLUS
CN Butanamide, 3-[(2-furanylmethyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



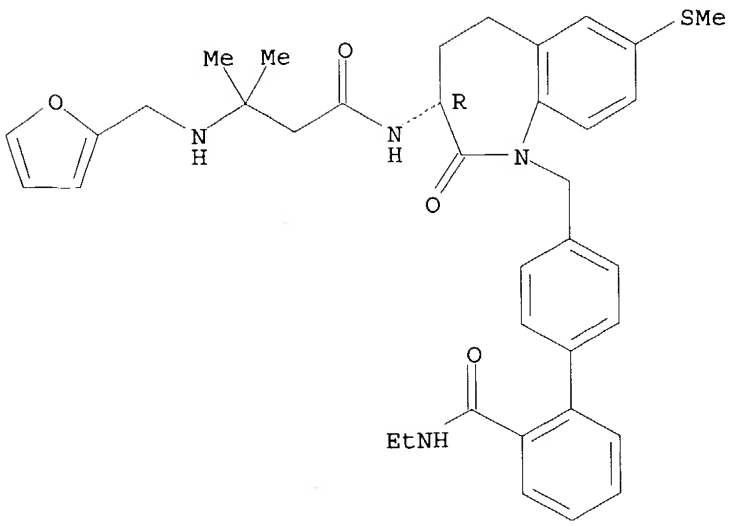
RN 169187-61-5 HCAPLUS
CN [1,1'-Biphenyl]-2-carboxamide, 4'-[[3-[[3-[(2-furanylmethyl)amino]-3-methyl-1-oxobutyl]amino]-2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1H-1-benzazepin-1-yl]methyl]-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 169187-66-0 HCAPLUS
CN [1,1'-Biphenyl]-2-carboxamide, N-ethyl-4'-[[3-[[3-[(2-furanylmethyl)amino]-3-methyl-1-oxobutyl]amino]-2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1H-1-benzazepin-1-yl]methyl]-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L52 ANSWER 12 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1995:867575 HCAPLUS
DOCUMENT NUMBER: 123:256776
ENTRY DATE: Entered STN: 20 Oct 1995
TITLE: Preparation of benzo-fused lactams which promote release of growth hormone.
INVENTOR(S): Schoen, William R.; Wyvratt, Matthew J., Jr.
PATENT ASSIGNEE(S): Merck and Co., Inc., USA
SOURCE: PCT Int. Appl., 131 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
INT. PATENT CLASSIF.:
MAIN: C07D281-10
SECONDARY: C07D223-16; C07D281-18; C07D223-06; A61K031-55
CLASSIFICATION: 28-22 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1, 27
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9503289	A1	19950202	WO 1994-US8195	19940720
W: AU, BB, BG, BR, BY, CA, CN, CZ, FI, GE, HU, JP, KE, KG, KR, KZ, LK, LT, LV, MD, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SI, SK, TJ, TT, UA, US, UZ				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5434261	A	19950718	US 1993-97149	19930726
AU 9474015	A1	19950220	AU 1994-74015	19940720
ZA 9405463	A	19950302	ZA 1994-5463	19940725
PRIORITY APPLN. INFO.:			US 1993-97149 A	19930726
			WO 1994-US8195 W	19940720

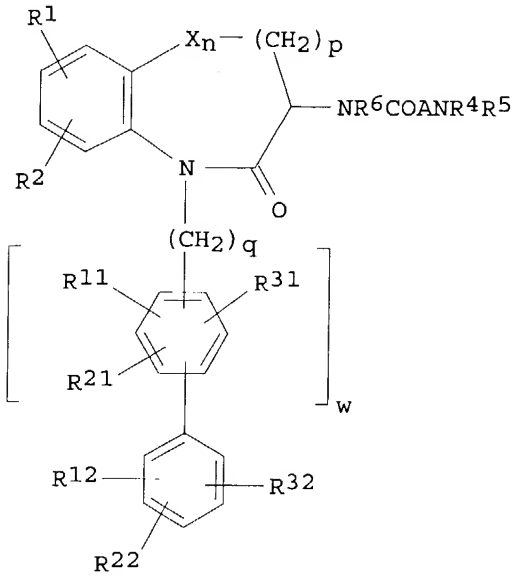
PATENT CLASSIFICATION CODES:

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES

WO 9503289	ICM	C07D281-10
	ICS	C07D223-16; C07D281-18; C07D223-06; A61K031-55
US 5434261	ECLA	C07D215/38C; C07D223/16B; C07D225/06; C07D267/14; C07D279/16; C07D281/10; C07D285/38; C07D040/12; C07D453/02; C07K005/06A1H

OTHER SOURCE(S): MARPAT 123:256776

GRAPHIC IMAGE:



I

ABSTRACT:
Title compds. [I; n, w = 0,1; p = 0-3; q = 0-4; X = CO, O, SOm, CH(OH), NR10, CH:CH; m = 0-2; R1, R2, R11, R12, R21, R22 = H, halo, alkyl, perfluoroalkyl, perfluoroalkoxy, cyano, NO2, (substituted) Ph, etc.; R31, R32 = H, R9, R9-substituted alkyl, Ph, PhO; R9 = R41R121NSO2(CH2)v, etc.; v = 1-3; R4, R5, R41 = H, (substituted) Ph, alkyl, alkenyl, alkynyl; R121 = R5, OR5, COR5, etc.; R4R5 = (CH2)rB(CH2)s; B = CHR1, O, SOm, NR10; r, s = 1-3; R6 = H, alkyl, Ph, phenylalkyl; A = (CH2)xCR8R81(CH2)y; x, y = 0-3; R8, R81 = H, alkyl, CF3, Ph (substituted) alkyl; R8R81 = (CH2)t; t = 2-6; R8, R81 can form alkylene bridges with R4 and/or R5], were prepared as promoters of the release of growth hormone in humans and animals (no data). Thus, 1-bromo-2-tert-butylbenzenesulfonamide (preparation given) and (4-methylphenyl)trimethylstannane (preparation given) were stirred with (Ph3P)2PdCl2 in DMF at 90° for 6 h to give 58% 4-methyl-2'-(tert-butylaminosulfonyl)-1,1'-biphenyl. This was refluxed with N-bromosuccinimide/azobisisobutyronitrile in CCl4 to give crude 4-bromomethyl-2'-(tert-butylaminosulfonyl)-1,1'-biphenyl. This was added to a mixture of 3-benzyloxycarbonylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3(R)-yl]butanamide and NaH in DMF and the mixture was stirred 12 h to give 46% 3-benzyloxycarbonylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(tert-butylamino)sulfonyl[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]butanamide. This was converted to title compound 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(benzamido)sulfonyl[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]butanamide trifluoroacetate.

SUPPL. TERM: biphenylylmethylbenzazepinone prepn growth hormone release

promoter; benzazepinone biphenylylmethyl acylamino growth hormone promoter; obesity treatment benzazepinone biphenylylmethyl acylamino; osteoporosis treatment benzazepinone biphenylylmethyl acylamino; benzothiazepinone biphenylylmethyl acylamino growth hormone promoter

INDEX TERM: Antiobesity agents
(benzo-fused lactam growth hormone release promoters with adrenergic agonists)

INDEX TERM: Peptides, biological studies
ROLE: AGR (Agricultural use); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(growth hormone releasing; GHRP-1, benzo-fused lactam growth hormone release promoters with other growth hormone secretagogues for increasing endogenous production of GH)

INDEX TERM: Peptides, biological studies
ROLE: AGR (Agricultural use); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(growth hormone releasing; GHRP-2, benzo-fused lactam growth hormone release promoters with other growth hormone secretagogues for increasing endogenous production of GH)

INDEX TERM: Osteoporosis
(treatment; benzo-fused lactam growth hormone release promoters with parathyroid hormone or a bisphosphonate)

INDEX TERM: Adrenergic antagonists
ROLE: AGR (Agricultural use); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(α2-, benzo-fused lactam growth hormone release promoters with adrenergic antagonists for treating obesity)

INDEX TERM: Adrenergic antagonists
ROLE: AGR (Agricultural use); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(β3-, benzo-fused lactam growth hormone release promoters with adrenergic antagonists for treating obesity)

INDEX TERM: 9034-39-3, Growth hormone releasing factor 36085-73-1, B-HT 920 67763-97-7, IGF-2 87616-84-0
ROLE: AGR (Agricultural use); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(benzo-fused lactam growth hormone release promoters with other growth hormone secretagogues for increasing endogenous production of GH)

INDEX TERM: 67763-96-6, IGF-1
ROLE: AGR (Agricultural use); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(benzo-fused lactam growth hormone release promoters with

other growth hormone secretagogues for increasing endogenous production of GH and treating the catabolic effects of nitrogen wasting)

INDEX TERM: 9002-64-6, Parathyroid hormone
ROLE: AGR (Agricultural use); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(benzo-fused lactam growth hormone release promoters with parathyroid hormone or a bisphosphonate for treating osteoporosis)

INDEX TERM: 161517-58-4P 161517-59-5P 161517-60-8P 169188-20-9P
169188-21-0P **169188-22-1P** 169188-23-2P
169188-24-3P 169188-25-4P 169188-26-5P
169188-27-6P 169188-28-7P 169188-29-8P
169188-30-1P 169188-31-2P **169188-32-3P**
169188-33-4P 169188-34-5P 169188-35-6P 169188-36-7P
169188-37-8P 169188-38-9P 169188-39-0P
169188-40-3P 169188-41-4P **169188-42-5P**
169188-43-6P 169188-44-7P 169188-45-8P 169188-46-9P
169188-47-0P 169188-48-1P 169188-49-2P
169188-50-5P 169188-51-6P **169188-52-7P**
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169188-57-2P 169188-58-3P 169188-59-4P
169188-60-7P **169188-61-8P** 169188-62-9P
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169188-69-6P 169188-70-9P **169188-71-0P**
169188-72-1P 169188-73-2P 169188-74-3P 169188-75-4P
169188-76-5P 169188-77-6P 169188-78-7P
169188-79-8P **169188-80-1P** 169188-81-2P
169188-82-3P 169188-83-4P 169188-84-5P
169188-85-6P 169188-86-7P 169188-87-8P
169188-88-9P 169188-89-0P **169188-90-3P**
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169189-70-2P 169189-71-3P 169189-72-4P 169189-73-5P
169189-74-6P 169189-75-7P 169189-76-8P 169189-84-8P
169189-85-9P
ROLE: AGR (Agricultural use); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic

use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of benzo-fused lactams which promote release of growth hormone)

INDEX TERM: 9002-72-6, Growth hormone
ROLE: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(preparation of benzo-fused lactams which promote release of growth hormone)

INDEX TERM: 65-85-0, Benzoic acid, reactions 75-64-9, tert-Butylamine, reactions 557-66-4, Ethylamine hydrochloride 1066-45-1, Trimethyltin chloride 2905-25-1, o-Bromobenzenesulfonyl chloride 4294-57-9, p-Tolylmagnesium bromide 145457-70-1 145485-77-4
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(preparation of benzo-fused lactams which promote release of growth hormone)

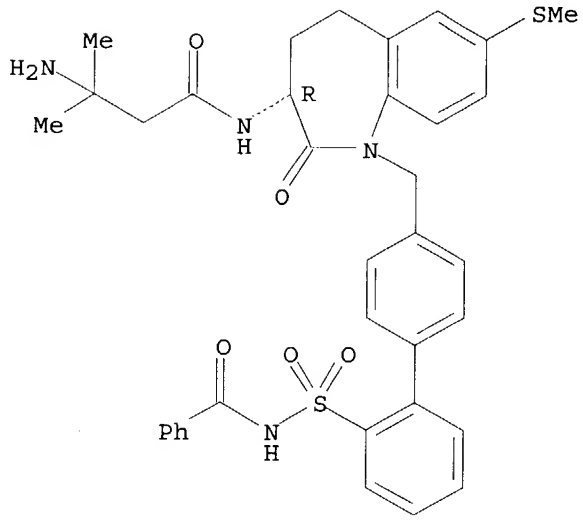
INDEX TERM: 937-12-2P 138733-50-3P 138733-51-4P 138733-52-5P 161517-55-1P 169189-78-0P 169189-79-1P 169189-80-4P 169189-81-5P 169189-82-6P 169189-83-7P
ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of benzo-fused lactams which promote release of growth hormone)

IT **169188-22-1P 169188-27-6P 169188-32-3P**
169188-37-8P 169188-42-5P 169188-47-0P
169188-52-7P 169188-57-2P 169188-61-8P
169188-66-3P 169188-71-0P 169188-76-5P
169188-80-1P 169188-85-6P 169188-90-3P
169188-95-8P
RL: AGR (Agricultural use); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of benzo-fused lactams which promote release of growth hormone)

RN 169188-22-1 HCAPLUS

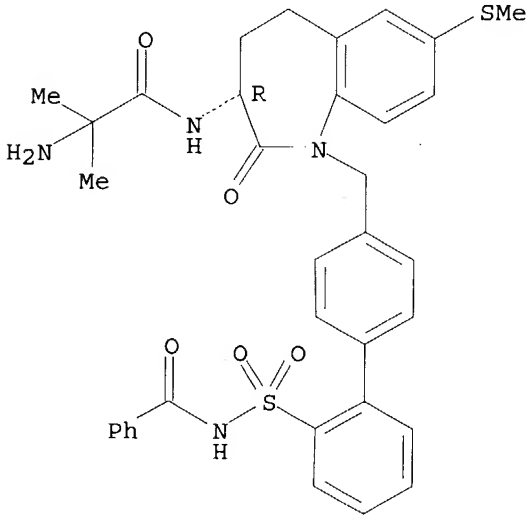
CN Benzamide, N-[[4'-[[3-[(3-amino-3-methyl-1-oxobutyl)amino]-2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1'-biphenyl]-2-yl]sulfonyl]-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



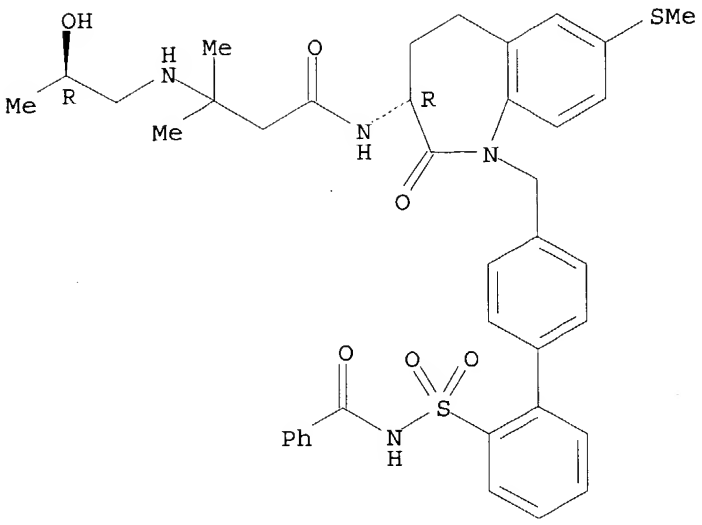
RN 169188-27-6 HCAPLUS
CN Benzamide, N-[[4'-[[3-[(2-amino-2-methyl-1-oxopropyl)amino]-2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1'-biphenyl]-2-yl]sulfonyl]-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



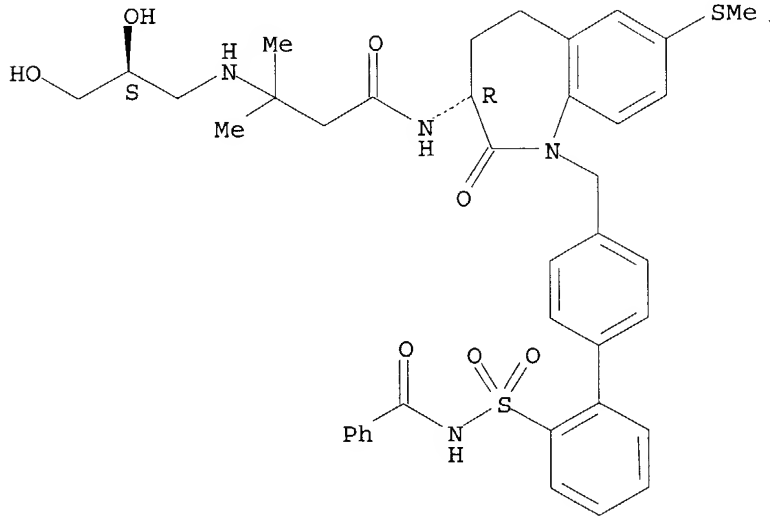
RN 169188-32-3 HCAPLUS
CN Benzamide, N-[[4'-[[2,3,4,5-tetrahydro-3-[[3-[(2-hydroxypropyl)amino]-3-methyl-1-oxobutyl]amino]-7-(methylthio)-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1'-biphenyl]-2-yl]sulfonyl]-, [R-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



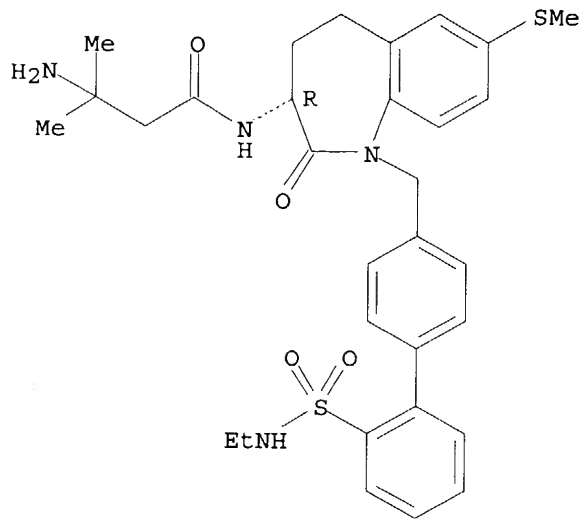
RN 169188-37-8 HCAPLUS
CN Benzamide, N-[[4'-[[3-[[3-[(2,3-dihydroxypropyl)amino]-3-methyl-1-oxobutyl]amino]-2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1'-biphenyl]-2-yl]sulfonyl]-, [S-(R*,S*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



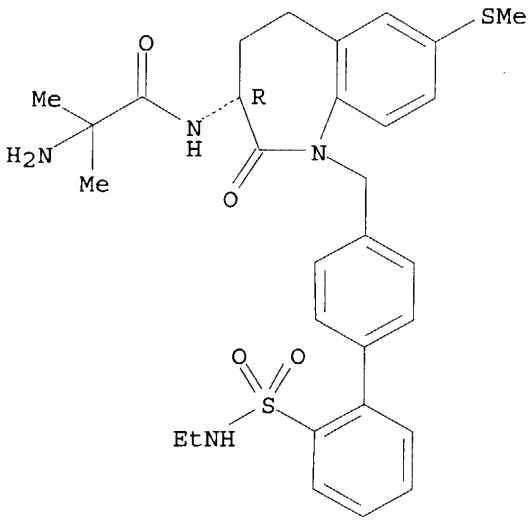
RN 169188-42-5 HCAPLUS
CN Butanamide, 3-amino-N-[1-[[2'-[(ethylamino)sulfonyl][1,1'-biphenyl]-4-yl]methyl]-2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-3-methyl-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



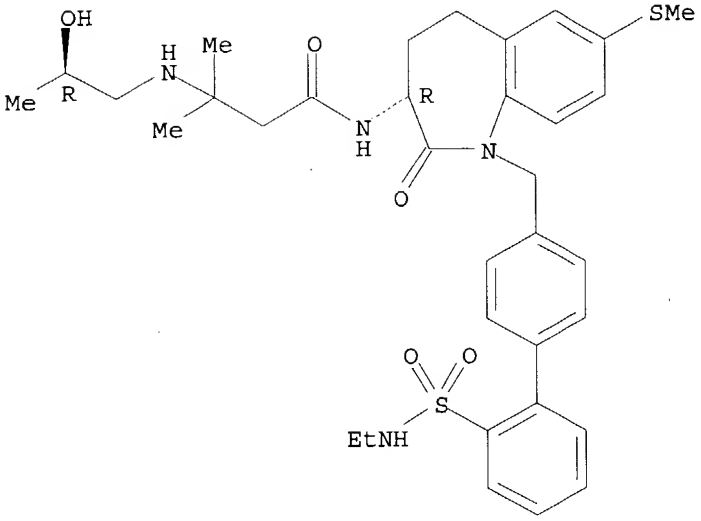
RN 169188-47-0 HCAPLUS
CN Propanamide, 2-amino-N-[1-[[2'-[(ethylamino)sulfonyl][1,1'-biphenyl]-4-yl]methyl]-2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-2-methyl-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



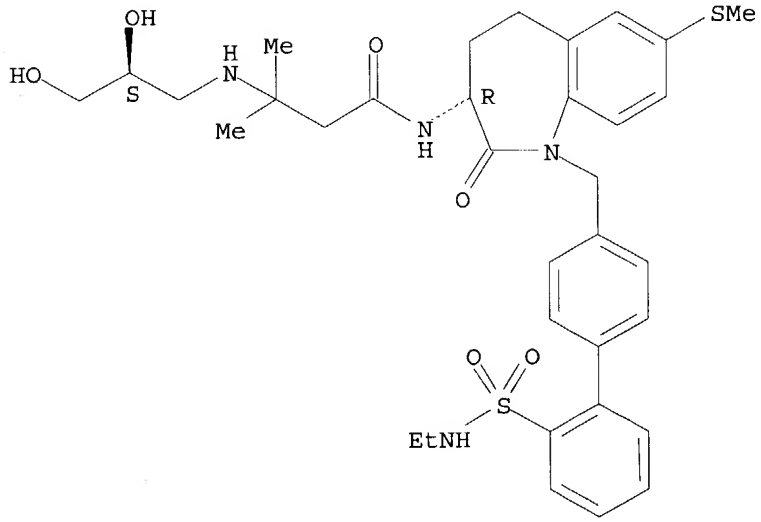
RN 169188-52-7 HCAPLUS
CN Butanamide, N-[1-[[2'-[(ethylamino)sulfonyl][1,1'-biphenyl]-4-yl]methyl]-2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-3-[(2-hydroxypropyl)amino]-3-methyl-, [R-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



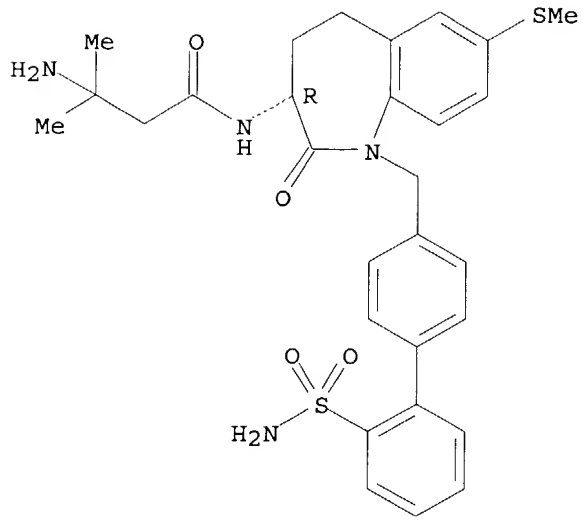
RN 169188-57-2 HCAPLUS
CN Butanamide, 3-[(2,3-dihydroxypropyl)amino]-N-[1-[[2'-[(ethylamino)sulfonyl][1,1'-biphenyl]-4-yl]methyl]-2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-3-methyl-, [S-(R*,S*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



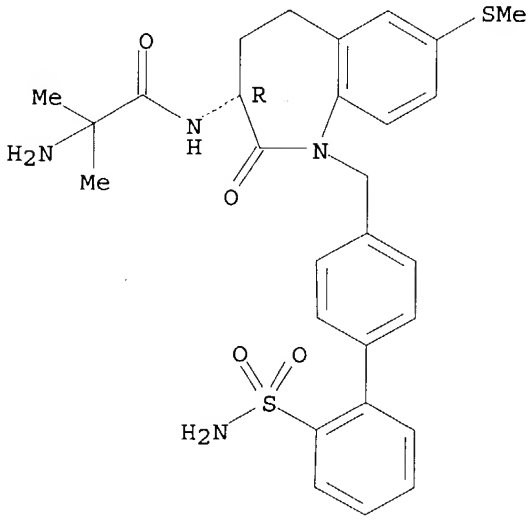
RN 169188-61-8 HCAPLUS
CN Butanamide, 3-amino-N-[1-[[2'-(aminosulfonyl)[1,1'-biphenyl]-4-yl]methyl]-2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-3-methyl-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



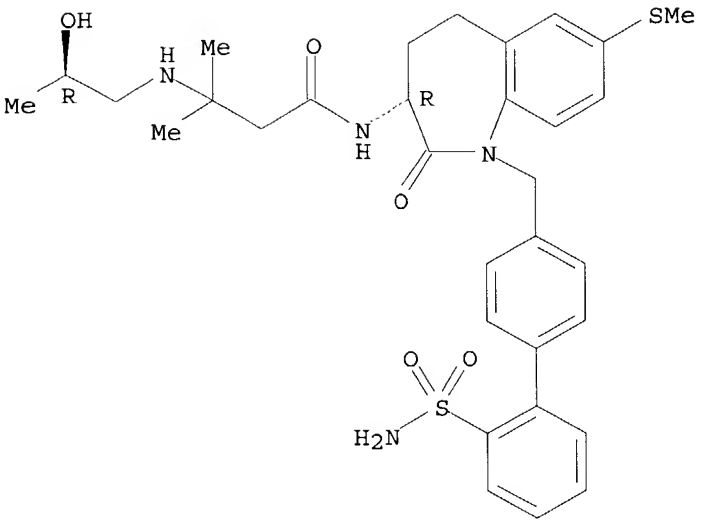
RN 169188-66-3 HCAPLUS
CN Propanamide, 2-amino-N-[1-[[2'-(aminosulfonyl)[1,1'-biphenyl]-4-yl]methyl]-2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-2-methyl-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



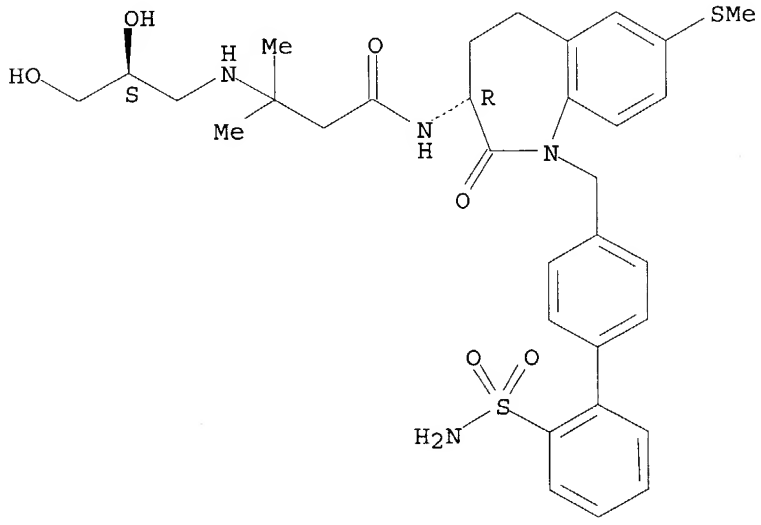
RN 169188-71-0 HCAPLUS
CN Butanamide, N-[1-[[2'-(aminosulfonyl)[1,1'-biphenyl]-4-yl]methyl]-2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-3-[(2-hydroxypropyl)amino]-3-methyl-, [R-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



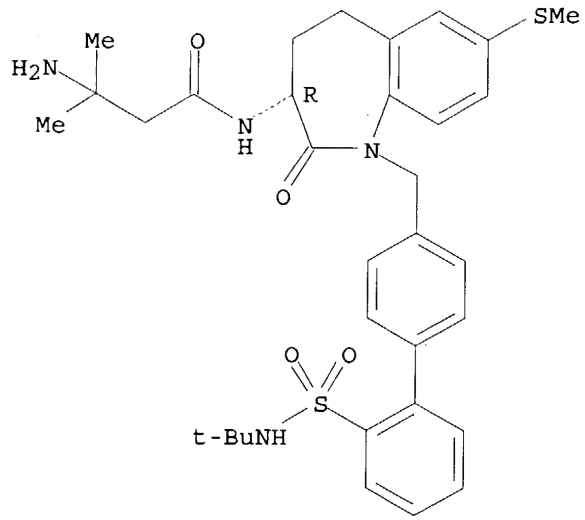
RN 169188-76-5 HCAPLUS
CN Butanamide, N-[1-[[2'-(aminosulfonyl)[1,1'-biphenyl]-4-yl]methyl]-2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-3-[(2,3-dihydroxypropyl)amino]-3-methyl-, [S-(R*,S*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 169188-80-1 HCAPLUS
CN Butanamide, 3-amino-N-[1-[[2'-[[(1,1-dimethylethyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-3-methyl-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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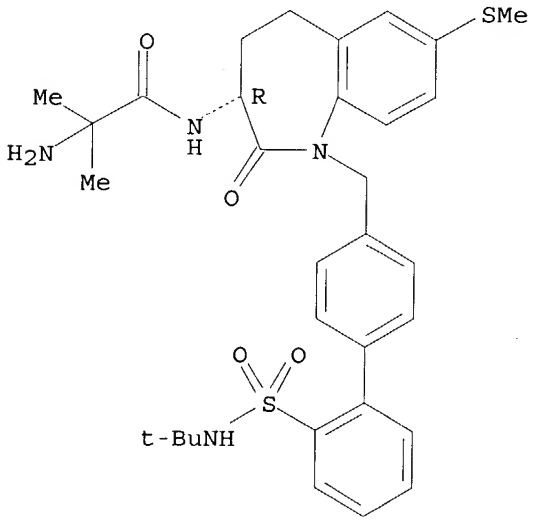
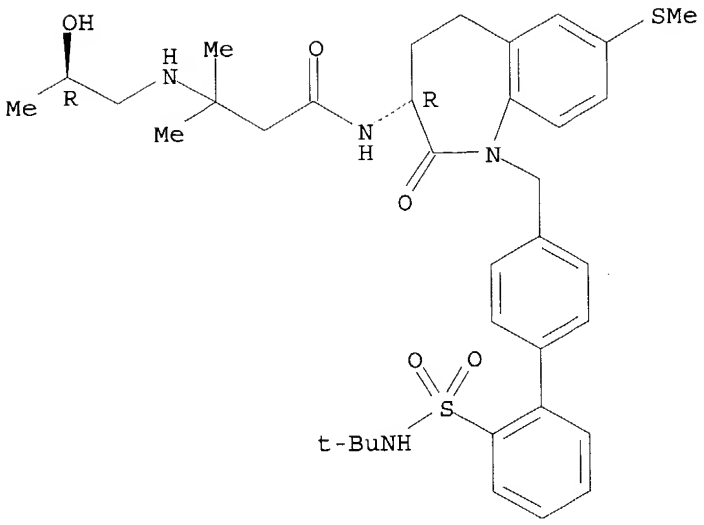
Absolute stereochemistry.



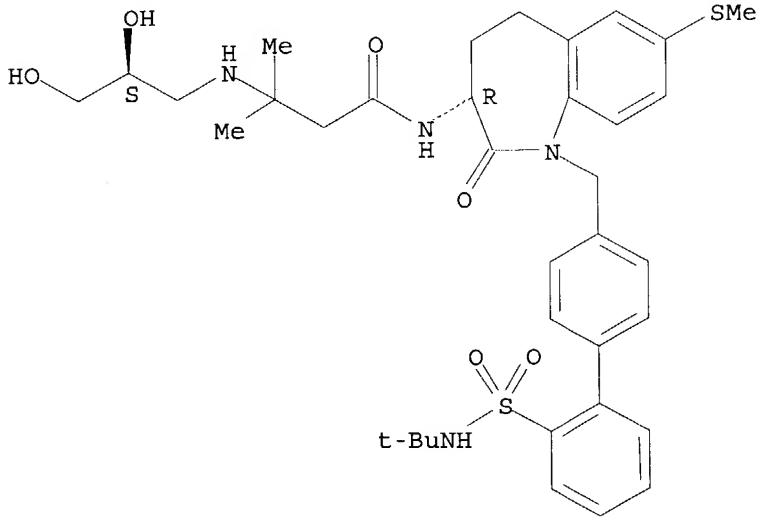
RN 169188-90-3 HCAPLUS
CN Butanamide, N-[1-[[2'-[[(1,1-dimethylethyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-3-[(2-hydroxypropyl)amino]-3-methyl-, [R-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 169188-95-8 HCAPLUS
CN Butanamide, 3-[(2,3-dihydroxypropyl)amino]-N-[1-[[2'-[[(1,1-dimethylethyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-3-methyl-, [S-(R*,S*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L52 ANSWER 13 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1995:792575 HCAPLUS
DOCUMENT NUMBER: 123:198644
ENTRY DATE: Entered STN: 15 Sep 1995
TITLE: Preparation of N-(N-heterocyclylbenzazepinyl)aminoalkanamides as growth hormone release promoters
INVENTOR(S): Schoen, William R.; Wyvratt, Matthew J.
PATENT ASSIGNEE(S): Merck and Co., Inc., USA

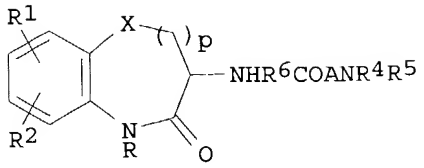
SOURCE: PCT Int. Appl., 174 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
INT. PATENT CLASSIF.:
MAIN: A61K031-555
SECONDARY: A61K031-395; C07D403-06; C07D401-06; C07D405-06; C07D413-06
CLASSIFICATION: 27-21 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 1
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9408583	A1	19940428	WO 1993-US9561	19931005
W: AU, BB, BG, BR, BY, CA, CZ, FI, HU, JP, KR, KZ, LK, LV, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SK, UA, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5374721	A	19941220	US 1992-961008	19921014
CA 2144764	AA	19940428	CA 1993-2144764	19931005
AU 9453226	A1	19940509	AU 1994-53226	19931005
AU 676223	B2	19970306		
EP 665750	A1	19950809	EP 1993-923288	19931005
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
JP 08502297	T2	19960312	JP 1993-510111	19931005
ZA 9307594	A	19940503	ZA 1993-7594	19931013
US 5726307	A	19980310	US 1994-356935	19941215
PRIORITY APPLN. INFO.:			US 1992-961008 A1	19921014
			WO 1993-US9561 W	19931005

PATENT CLASSIFICATION CODES:

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 9408583	ICM	A61K031-555
	ICS	A61K031-395; C07D403-06; C07D401-06; C07D405-06; C07D413-06
US 5374721	ECLA	C07D403/06; C07D403/14; C07D405/06; C07D405/14; C07D049/06; C07D409/14; C07D413/06

OTHER SOURCE(S): MARPAT 123:198644
GRAPHIC IMAGE:



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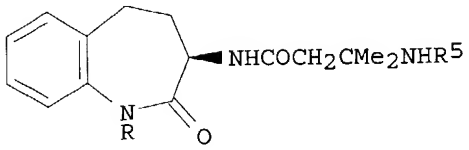
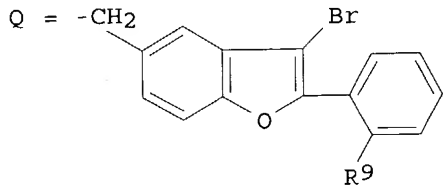


II



ABSTRACT:
Title compds. [I; A = (un)substituted alkylene; R = (CH2)qLR7; L = (un)substituted divalent benzo-fused heterocyclyl; R1,R2 = H, halo, (perfluoro)alkyl, Ph, etc.; R4,R5 = H, alkyl, Ph, etc.; R6 = H, alkyl, phenyl(alkyl); R7 = (un)substituted Ph; X = CO, O, SO0-2, CH(OH), CH:CH, etc.; n = 0 or 1; p = 0-3; q = 0-4] were prepared as growth hormone release promoters (no data). Thus, 1-tetralone was converted in 5 steps to 3(R)-amino-2,3,4,5-tetrahydro-1H-benzazepin-2-one which was amidated by HO2CCH2CMe2NHBOC (preparation given) to give benzazepinylaminoalkanamide II (R = H, R5 = BOC) which was N-alkylated by BrCH2LR7 (CH2LR7 = benzofuranylmethyl group Q, R9 = trityl-protected 5-tetrazolyl) to give, after deprotection, II (R = Q, R5 = H, R9 = 5-tetrazolyl).

SUPPL. TERM: benzazepinylaminoalkanamide growth hormone release

INDEX TERM: Antiobesity agents
(preparation of N-(N-heterocyclylbenzazepinyl)aminoalkanamides as growth hormone release promoters)

INDEX TERM: Osteoporosis
(treatment; preparation of N-(N-heterocyclylbenzazepinyl)amino alkanamides as growth hormone release promoters)

INDEX TERM: 613-84-3P 3349-64-2P, 1-Tetralone oxime 4424-80-0P
4879-95-2P 86499-35-6P 129765-95-3P 137036-55-6P
140700-64-7P 143381-79-7P 143381-80-0P 143381-81-1P
145457-69-8P 145485-77-4P 145486-33-5P 145486-47-1P
155300-46-2P 160278-26-2P 164802-91-9P 167710-92-1P
167710-93-2P 167823-28-1P
ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; preparation of N-(N-heterocyclylbenzazepinyl)aminoalkanamides as growth hormone release promoters)

INDEX TERM: 167822-21-1P 167822-22-2P 167822-23-3P 167822-24-4P
167822-25-5P 167822-26-6P 167822-27-7P 167822-28-8P
167822-29-9P 167822-30-2P 167822-31-3P 167822-32-4P
167822-33-5P 167822-34-6P 167822-35-7P 167822-36-8P
167822-37-9P 167822-38-0P 167822-39-1P 167822-40-4P

167822-41-5P 167822-42-6P 167822-43-7P 167822-44-8P
167822-45-9P 167822-46-0P 167822-47-1P 167822-48-2P
167822-49-3P 167822-50-6P 167822-51-7P 167822-52-8P
167822-53-9P 167822-54-0P 167822-55-1P 167822-56-2P
167822-57-3P 167822-58-4P 167822-59-5P 167822-60-8P
167822-61-9P 167822-62-0P 167822-63-1P 167822-64-2P
167822-65-3P 167822-66-4P 167822-67-5P 167822-68-6P
167822-69-7P 167822-70-0P 167822-71-1P 167822-72-2P
167822-73-3P **167822-74-4P** 167822-75-5P
167822-76-6P 167822-77-7P 167822-78-8P 167822-79-9P
167822-80-2P 167822-81-3P 167822-82-4P 167822-83-5P
167822-84-6P 167822-85-7P 167822-86-8P 167822-87-9P
167822-88-0P 167822-89-1P 167822-90-4P 167822-91-5P
167822-92-6P 167822-93-7P 167822-94-8P 167822-95-9P
167822-96-0P **167822-97-1P** 167822-98-2P
167822-99-3P 167823-00-9P 167823-01-0P 167823-02-1P
167823-03-2P 167823-04-3P 167823-05-4P 167823-06-5P
167823-07-6P 167823-08-7P 167823-09-8P 167823-10-1P
167823-11-2P 167823-12-3P 167823-13-4P 167823-14-5P
167823-15-6P 167823-16-7P 167823-17-8P 167823-18-9P
167823-19-0P 167823-20-3P 167823-21-4P 167823-22-5P
167823-23-6P 167823-24-7P 167823-25-8P 167823-26-9P
ROLE: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of N-(N-heterocyclylbenzazepinyl)aminoalkanamides as growth hormone release promoters)

INDEX TERM: 9002-72-6, Growth hormone
ROLE: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)
(preparation of N-(N-heterocyclylbenzazepinyl)aminoalkanamides as growth hormone release promoters)

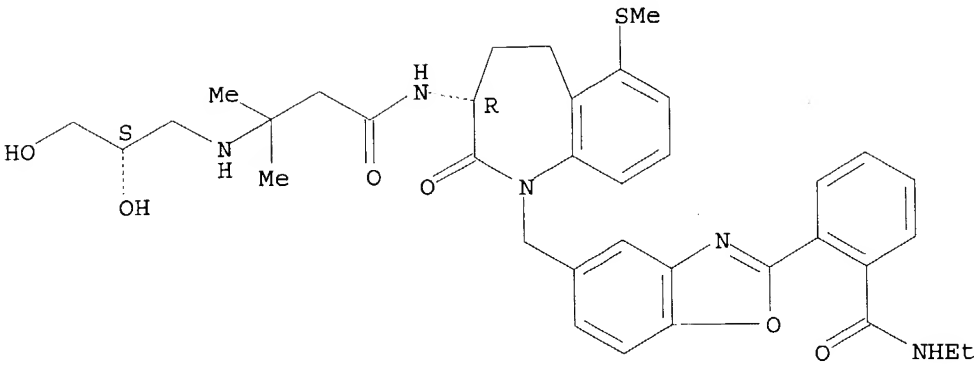
INDEX TERM: 106-44-5, reactions 115-11-7, reactions 529-34-0, 1-Tetralone 22115-41-9, α-Bromo-o-tolunitrile 81445-45-6
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(starting material; preparation of N-(N-heterocyclylbenzazepinyl)aminoalkanamides as growth hormone release promoters)

IT **167822-74-4P 167822-97-1P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of N-(N-heterocyclylbenzazepinyl)aminoalkanamides as growth hormone release promoters)

RN 167822-74-4 HCAPLUS

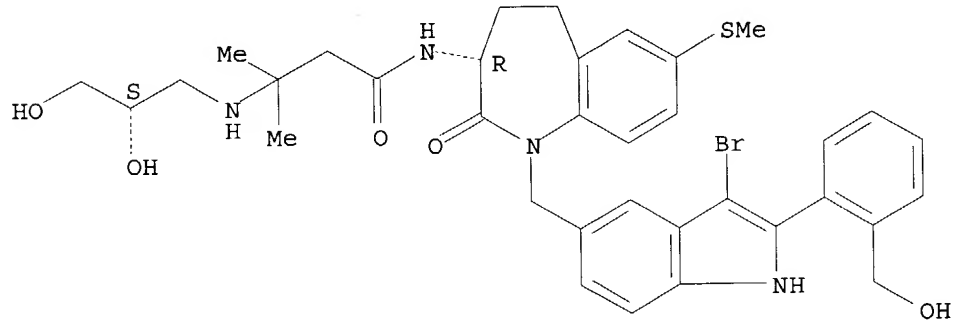
CN Benzamide, 2-[5-[[3-[[3-[(2,3-dihydroxypropyl)amino]-3-methyl-1-oxobutyl]amino]-2,3,4,5-tetrahydro-6-(methylthio)-2-oxo-1H-1-benzazepin-1-yl]methyl]-2-benzoxazolyl]-N-ethyl-, [S-(R*,S*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 167822-97-1 HCAPLUS
CN Butanamide, N-[1-[[3-bromo-2-[2-(hydroxymethyl)phenyl]-1H-indol-5-yl]methyl]-2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-3-[(2,3-dihydroxypropyl)amino]-3-methyl-, [S-(R*,S*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L52 ANSWER 14 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1995:9058 HCAPLUS
DOCUMENT NUMBER: 122:160643
ENTRY DATE: Entered STN: 08 Nov 1994
TITLE: Benzo-fused lactams which promote the release of growth hormone
INVENTOR(S): Ok, Ok Hyun; Schoen, William R.; Wyvratt, Matthew J.
PATENT ASSIGNEE(S): Merck and Co., Inc., USA
SOURCE: PCT Int. Appl., 133 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
INT. PATENT CLASSIF.:
MAIN: A61K031-33
SECONDARY: A61K031-55; C07D223-16; C07D225-06; C07D261-20; C07D267-02; C07D267-22; C07D281-02; C07D281-18
CLASSIFICATION: 28-10 (Heterocyclic Compounds (More Than One Hetero Atom))
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

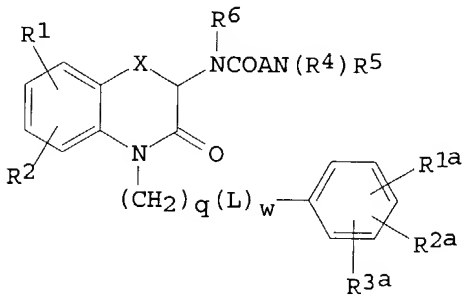
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9407483	A1	19940414	WO 1993-US8894	19930921
W: AU, BB, BG, BR, BY, CA, CZ, FI, HU, JP, KR, KZ, LK, LV, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SK, UA, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5317017	A	19940531	US 1992-954220	19920930
EP 665747	A1	19950809	EP 1993-922263	19930921
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
JP 08502252	T2	19960312	JP 1993-509125	19930921
AU 676501	B2	19970313	AU 1993-51327	19930921
AU 9351327	A1	19940426		
ZA 9307222	A	19940420	ZA 1993-7222	19930929
PRIORITY APPLN. INFO.:			US 1992-954220 A1	19920930
			WO 1993-US8894 W	19930921

PATENT CLASSIFICATION CODES:

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 9407483	ICM	A61K031-33
	ICS	A61K031-55; C07D223-16; C07D225-06; C07D261-20; C07D267-02; C07D267-22; C07D281-02; C07D281-18

OTHER SOURCE(S): MARPAT 122:160643

GRAPHIC IMAGE:



I

ABSTRACT:
The title compds. [I; A = (un)substituted alkylene; L = (un)substituted phenylene; R1, R1a, R2, R2a = H, halogen, C1-7 alkyl CN, NO2, (un)substituted Ph, etc.; R3a = H, (un)substituted C1-6 alkyl or Ph; R4, R5 = H, (un)substituted Ph, (un)substituted alkyl, alkenyl, alkynyl, etc.; R6 = H, C1-10 alkyl, Ph, phenyl-substituted alkyl; X = (un)substituted CH2CH2, (un)substituted CH:CH, etc.; q = 0-4; w = 0, 1], which promote the release the growth hormone (no data), are prepared Thus, 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-4-(4-methoxyphenyl)-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]butanamide trifluoroacetate was prepared from 2,3,4,5-tetrahydro-3-(methoxycarbonyl)-4-(4-methoxyphenyl)-1H-1-benzazepin-2-one in 14 steps.

SUPPL. TERM: tetrazolylbenzazepine growth hormone release stimulator

INDEX TERM: Lactams
ROLE: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(benzo-fused, preparation of, as growth hormone release

accelerators)

INDEX TERM: 9002-72-6, Growth hormone
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(accelerated secretion of, benzo-fused lactams for)

INDEX TERM: 158103-83-4 158103-91-4 158103-93-6 158103-96-9
158103-99-2 158104-07-5 158104-08-6 158104-09-7
158104-10-0 **158104-11-1**
158104-12-2 158104-13-3 158104-14-4
158104-15-5 158104-16-6 158104-17-7 158104-18-8
158104-19-9 158104-20-2 **158104-21-3**
158104-22-4 158104-23-5 158104-24-6 158104-25-7
158104-26-8 158104-27-9 158104-28-0 158104-29-1
158104-30-4 **158104-31-5** 158104-32-6
158104-33-7 158104-34-8 158104-35-9 158104-36-0
158104-37-1 158104-38-2 158104-39-3 158104-40-6
158104-41-7 **158104-42-8** 158104-43-9
158104-44-0 158104-45-1 158104-46-2 158104-47-3
158104-48-4 158104-49-5 158104-50-8 158104-51-9
158104-52-0 158104-53-1 158104-54-2 158104-55-3
158104-56-4 158104-57-5 158104-58-6 158104-59-7
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158104-68-8 158104-69-9 158104-70-2 158104-71-3
158104-72-4 158104-73-5 158104-74-6 158104-75-7
158104-76-8 158104-77-9 158104-78-0 158104-79-1
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158104-84-8 158104-85-9 158104-86-0 158104-87-1
158104-88-2 158104-89-3 158104-90-6 158104-91-7
158104-92-8 158104-93-9 158104-94-0 158104-95-1
158124-30-2
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(growth hormone release accelerator)

INDEX TERM: 9034-39-3, Growth hormone releasing factor 36085-73-1,
B-HT 920 67763-96-6, Insulin-like growth factor I
67763-97-7, Insulin-like growth factor II 87616-84-0, GHRP
6
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(growth hormone secretagogue, benzo-fused lactams for
formulation with)

INDEX TERM: 4879-95-2P 18039-42-4P 87268-78-8P 104479-28-9P
129765-95-3P 133051-88-4P 133909-97-4P 155300-46-2P
158103-85-6P 158103-86-7P 158103-87-8P 158103-88-9P
158103-89-0P 158103-90-3P 158103-98-1P 158104-01-9P
158104-02-0P 158104-06-4P
ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP
(Preparation); RACT (Reactant or reagent)
(preparation and reaction of, in preparation of growth hormone
release accelerators)

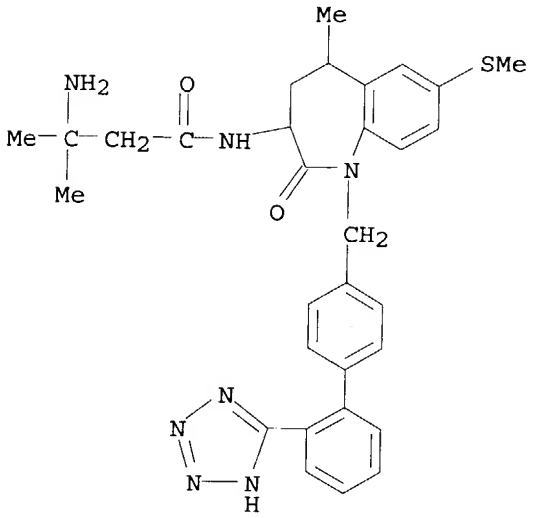
INDEX TERM: 158103-84-5P 158103-92-5P 158103-94-7P 158103-97-0P
158104-00-8P 158104-04-2P
ROLE: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, as growth hormone release accelerator)

INDEX TERM: 76-83-5, Triphenylmethyl chloride 100-47-0, Benzonitrile,
reactions 115-11-7, Isobutylene, reactions 624-31-7,
4-Iodotoluene 16029-98-4, Trimethylsilyl iodide
19832-98-5, 4-Methyl-1-tetralone 24424-99-5, Di-tert-butyl
dicarbonate 27068-88-8 81445-45-6 107967-07-7
158103-95-8
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, in preparation of growth hormone release

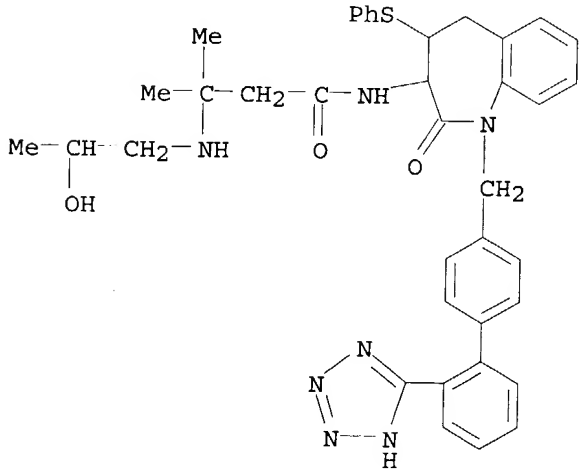
accelerators)

IT **158104-10-0 158104-11-1 158104-12-2**
158104-21-3 158104-31-5 158104-42-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(growth hormone release accelerator)

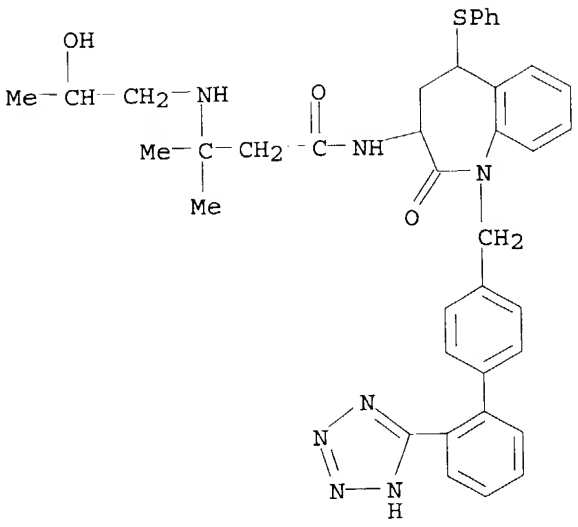
RN 158104-10-0 HCAPLUS
CN Butanamide, 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-5-methyl-7-(methylthio)-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]- (9CI) (CA INDEX NAME)



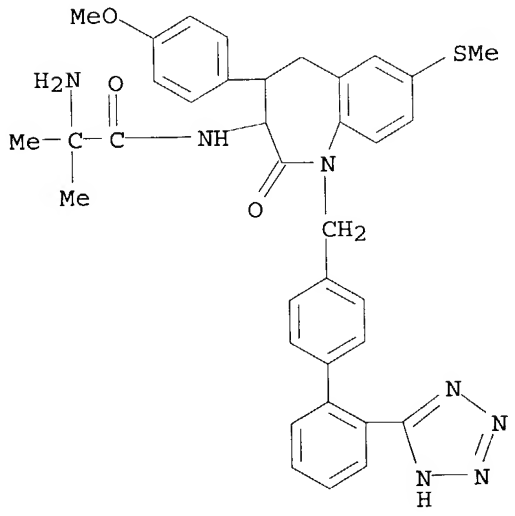
RN 158104-11-1 HCAPLUS
CN Butanamide, 3-[(2-hydroxypropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-4-(phenylthio)-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]- (9CI) (CA INDEX NAME)



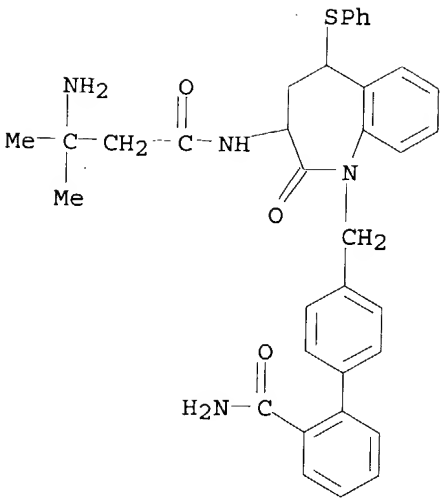
RN 158104-12-2 HCAPLUS
CN Butanamide, 3-[(2-hydroxypropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-5-(phenylthio)-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]- (9CI) (CA INDEX NAME)



RN 158104-21-3 HCAPLUS
CN Propanamide, 2-amino-2-methyl-N-[2,3,4,5-tetrahydro-4-(4-methoxyphenyl)-7-(methylthio)-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]- (9CI) (CA INDEX NAME)



RN 158104-31-5 HCAPLUS
CN [1,1'-Biphenyl]-2-carboxamide, 4'-[[3-[(3-amino-3-methyl-1-oxobutyl)amino]-2,3,4,5-tetrahydro-2-oxo-5-(phenylthio)-1H-1-benzazepin-1-yl]methyl]- (9CI) (CA INDEX NAME)



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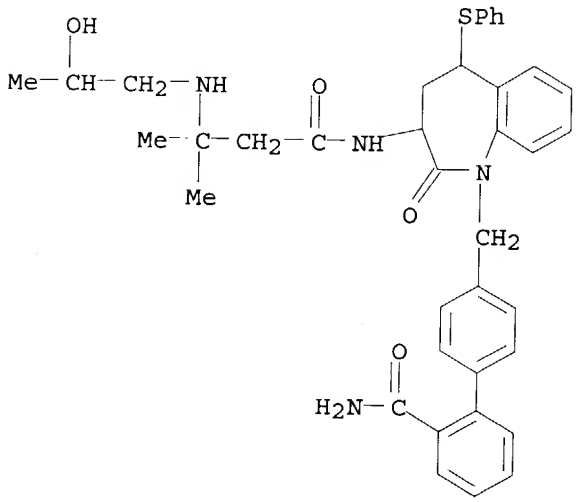
CN [1,1'-Biphenyl]-2-carboxamide, 4'-[[2,3,4,5-tetrahydro-3-[[3-[(2-hydroxypropyl)amino]-3-methyl-1-oxobutyl]amino]-2-oxo-5-(phenylthio)-1H-1-benzazepin-1-yl]methyl]- (9CI) (CA INDEX NAME)



L52 ANSWER 15 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1993:169109 HCAPLUS
DOCUMENT NUMBER: 118:169109
ENTRY DATE: Entered STN: 01 May 1993
TITLE: Preparation of (tetrazolylbiphenylmethyl)benzazepinones and related compounds as growth hormone release promoters
INVENTOR(S): Fisher, Michael H.; Wyvratt, Matthew J.; Schoen, William R.; Devita, Robert J.
PATENT ASSIGNEE(S): Merck and Co., Inc., USA
SOURCE: PCT Int. Appl., 346 pp.
CODEN: PIXXD2

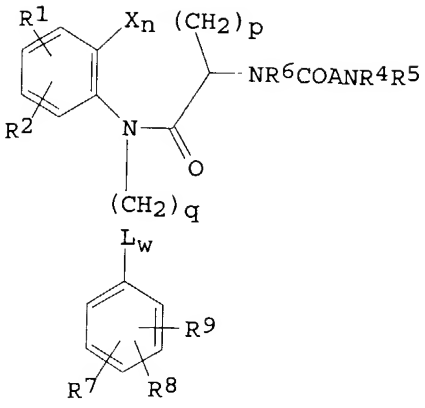
DOCUMENT TYPE: Patent
LANGUAGE: English
INT. PATENT CLASSIF.:
MAIN: C07D403-10
SECONDARY: C07D223-16; C07D401-10; C07D417-10; C07D227-10; C07K005-06; C07D281-10; A61K031-33
CLASSIFICATION: 28-10 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1, 34
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9216524	A1	19921001	WO 1992-US2271	19920319
W: BB, BG, BR, LK, MG, MN, MW, PL, RO, RU, SD				
US 5206235	A	19930427	US 1992-839742	19920228
EP 513974	A1	19921119	EP 1992-302143	19920312
EP 513974	B1	19960904		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, PT, SE				
AT 142206	E	19960915	AT 1992-302143	19920312
IL 101206	A1	19970218	IL 1992-101206	19920312
CA 2063185	AA	19920921	CA 1992-2063185	19920317
NO 9201077	A	19920921	NO 1992-1077	19920319
AU 9213012	A1	19920924	AU 1992-13012	19920319
AU 653992	B2	19941020		
CN 1066070	A	19921111	CN 1992-102954	19920319
CN 1033584	B	19961218		
ZA 9202009	A	19921125	ZA 1992-2009	19920319
JP 06172316	A2	19940621	JP 1992-112069	19920319
JP 08000814	B4	19960110		
HU 66796	A2	19941228	HU 1992-915	19920319
RO 117326	B1	20020130	RO 1993-1245	19920319
US 5310737	A	19940510	US 1993-12190	19930202
PRIORITY APPLN. INFO.:			US 1991-673695 A	19910320
			US 1992-839742 A	19920228
			WO 1992-US2271 W	19920319

PATENT CLASSIFICATION CODES:

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 9216524	ICM	C07D403-10
	ICS	C07D223-16; C07D401-10; C07D417-10; C07D227-10; C07K005-06; C07D281-10; A61K031-33

OTHER SOURCE(S): MARPAT 118:169109
GRAPHIC IMAGE:



I

ABSTRACT:
Title compds. [I; L = (substituted) phenylene; n, w = 0, 1; p = 0-3; q = 0-4; X = CO, O, S, SO, SO2, CH(OH), CH:CH, imino; R1, R2, R7, R8 = H, halo, (perfluoro)alkyl, perfluoroalkoxy, cyano, NO2, (substituted) Ph, acyl(alkyl), etc.; R4, R5 = H, (substituted) Ph, alkyl, alkenyl, alkynyl, alkanoyloxy, alkoxycarbonyl, carboxy, CHO, amino; R4R5 = (CH2)rB(CH2)s; B = CH2, O, imino, S, SO, SO2; r, s = 1-3; R6 = H, alkyl, Ph, phenylalkyl; R9 = H, (substituted) tetrazolyl, acylalkyl, aminoalkyl, carbamoylalkyl, tetrazolylalkyl, tetrazolylphenyl, tetrazolylphenoxy, etc.; A = (CH2)xCR10R11(CH2)y; x, y = 0-3; R10, R11 = H, CF3, (substituted) alkyl, Ph, etc.; R10R11 = (CH2)t; t = 2-6; R10, R11 may be joined to R4 and/or R5], were prepared for promotion of release of growth hormone (no data). Thus, 3-benzyloxycarbonylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3R-yl]butanamide (preparation from 3-azido-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one given) was stirred 15 min with NaH in DMF; N-triphenylmethyl-5-[2-(4'-bromobiphen-4-yl)]tetrazole (preparation starting from 5-phenyl-2-trityltetrazole and 4-IC6H4Me given) in DMF was added and the mixture was stirred 90 min to give 95% coupling product, which was hydrogenated in MeOH over Pd(OH)2/C for 14 h to give 89% 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3R-yl]butanamide trifluoroacetate.

SUPPL. TERM: biphenylmethyloxobenzazepinamide growth hormone release; benzazepinamide prepn growth hormone release

INDEX TERM:

145455-23-8P	145455-24-9P	145455-25-0P	145455-26-1P
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ROLE: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of, as growth hormone release promoter)

INDEX TERM: 145486-79-9
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(preparation of, as intermediate for growth hormone release promoter)

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ROLE: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, as intermediate for growth hormone release promoter)

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ROLE: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, as intermediate for growth hormone release promoter)

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100-46-9, Benzenemethanamine, reactions 100-47-0,
Benzonitrile, reactions 100-52-7, Benzaldehyde, reactions
100-79-8 103-63-9 108-59-8 109-89-7, reactions
115-18-4 123-38-6, Propanal, reactions 141-43-5,
reactions 306-23-0 392-83-6 455-01-6 498-94-2,
4-Piperidinecarboxylic acid 529-34-0 557-66-4 577-19-5

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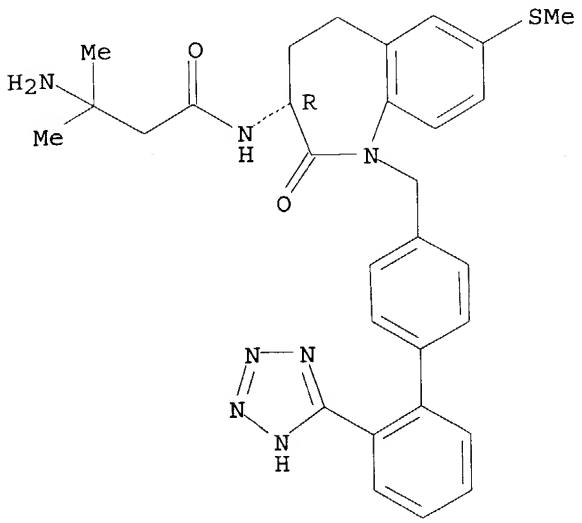
145486-66-4 145486-67-5
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, in preparation of growth hormone release promoter)

INDEX TERM: 9002-72-6, Growth hormone
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(release promoters, benzazepinamides and related compds.)

IT **145455-70-5P 145455-71-6P 145455-72-7P**
145455-73-8P 145552-97-2P 145552-98-3P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of, as growth hormone release promoter)

RN 145455-70-5 HCAPLUS
CN Butanamide, 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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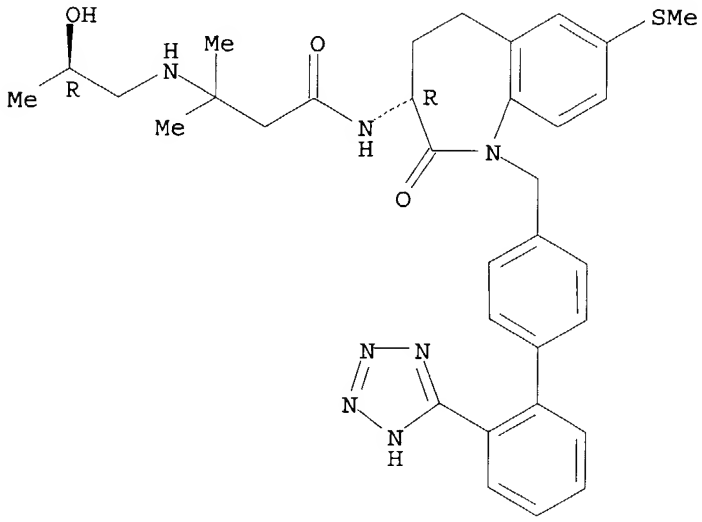
CN Butanamide, 3-[(2-hydroxypropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-

1H-1-benzazepin-3-yl]-, [R-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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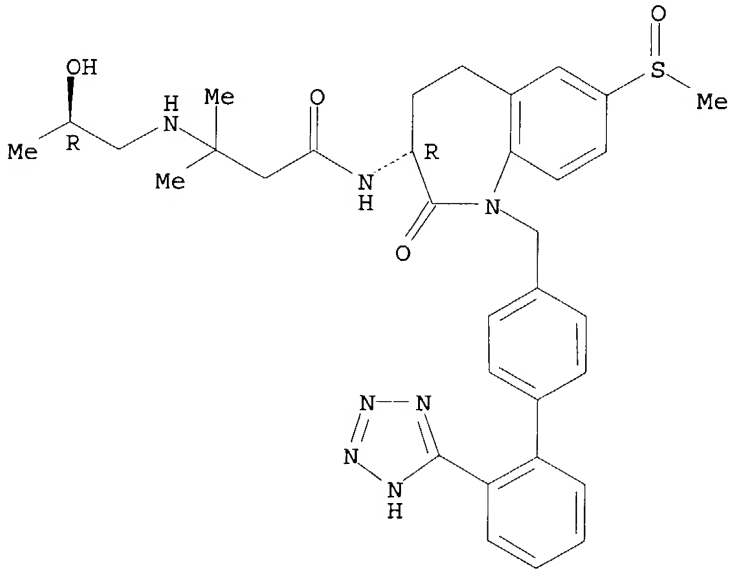
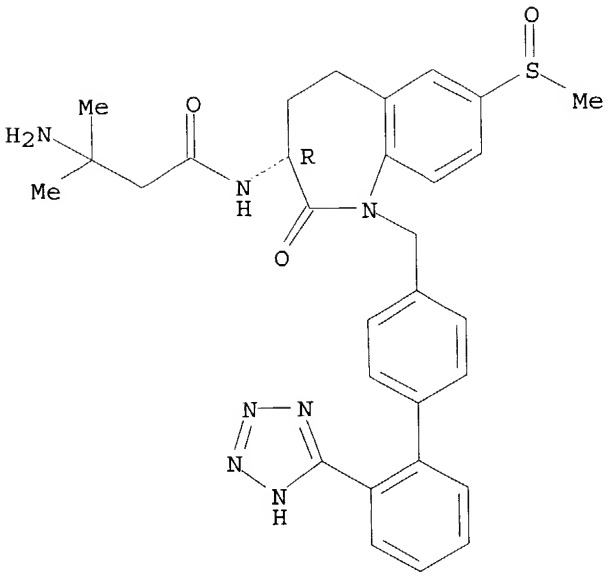
Absolute stereochemistry.

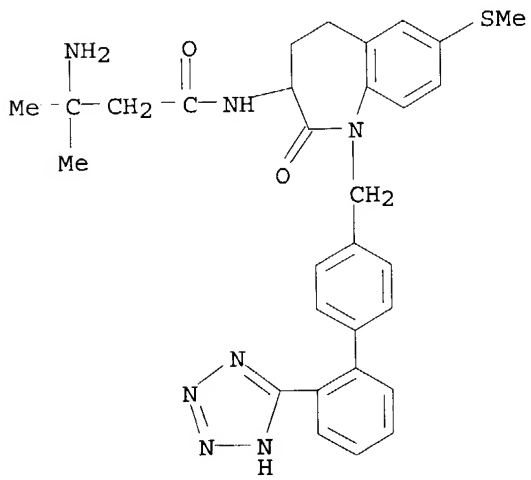


RN 145455-73-8 HCAPLUS
CN Butanamide, 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-7-(methylsulfinyl)-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-, (3R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

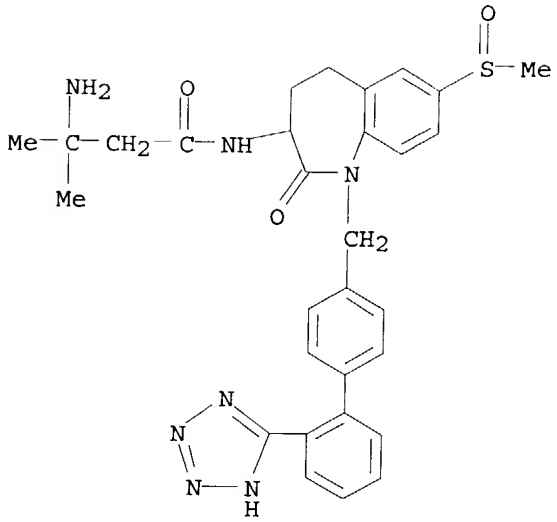


RN 145552-97-2 HCAPLUS
CN Butanamide, 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-, hydrochloride (9CI) (CA INDEX NAME)



●x HCl

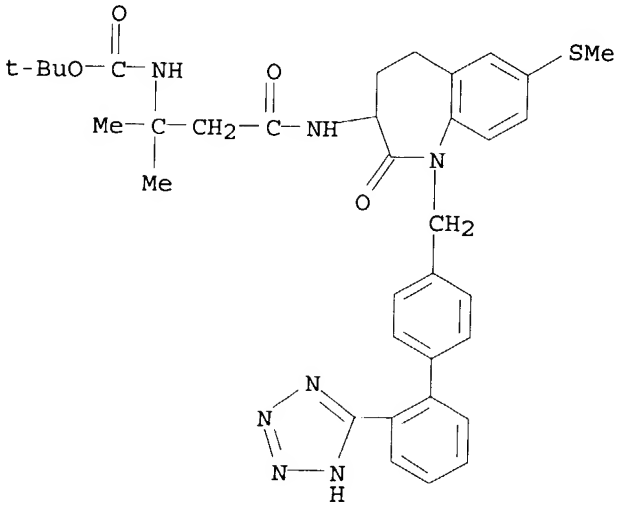
RN 145552-98-3 HCAPLUS
CN Butanamide, 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-7-(methylsulfinyl)-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-, hydrochloride (9CI) (CA INDEX NAME)



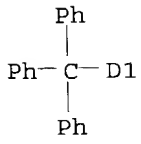
● x HCl

IT **146429-18-7P 146429-19-8P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, as intermediate for growth hormone release promoter)
RN 146429-18-7 HCAPLUS
CN Carbamic acid, [1,1-dimethyl-3-oxo-3-[[2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1-[[2'-[(triphenylmethyl)-1H(or 2H)-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]amino]propyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

PAGE 1-A

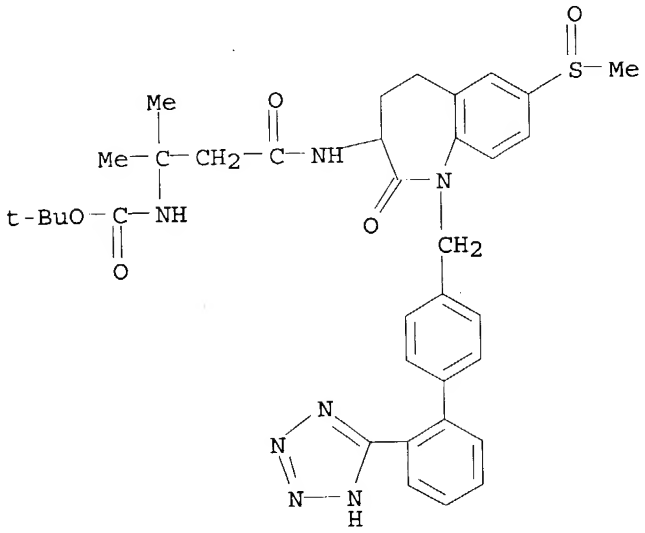


PAGE 2-A

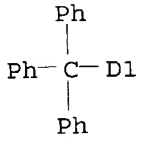


RN 146429-19-8 HCAPLUS
CN Carbamic acid, [1,1-dimethyl-3-oxo-3-[[2,3,4,5-tetrahydro-7-(methylsulfinyl)-2-oxo-1-[[2'-[(triphenylmethyl)-1H(or 2H)-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]amino]propyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

PAGE 1-A



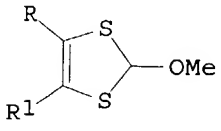
PAGE 2-A



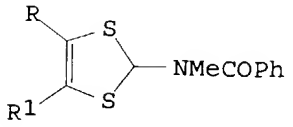
L52 ANSWER 16 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1986:442683 HCAPLUS
DOCUMENT NUMBER: 105:42683
ENTRY DATE: Entered STN: 09 Aug 1986
TITLE: Insertion of 1,3-dithiolium carbenes into the nitrogen-hydrogen bond of amides and imides
AUTHOR(S): Buza, Daniela; Gradowska, Wanda
CORPORATE SOURCE: Dep. Org. Chem., Polytech. Univ., Warsaw, 00664, Pol.
SOURCE: Polish Journal of Chemistry (1984), 58(10-12), 1059-69
CODEN: PJCHDQ; ISSN: 0137-5083
DOCUMENT TYPE: Journal
LANGUAGE: English

CLASSIFICATION: 28-5 (Heterocyclic Compounds (More Than One Hetero Atom))

GRAPHIC IMAGE:



I



II

ABSTRACT:
1,3-Dithiolium carbenes generated from 2-methoxy-1,3-dithioles I (R = R1 = Me, Ph; R = Ph, R1 = H; RR1 = CH:CHCH:CH) were inserted into the N-H bond of N-methylbenzamide, acetanilide, and succinimide to form N-(1,3-dithiol-2-yl)amides (imides), e.g. II, resp. N-Tosylacetamide and caprolactam were not suitable as trapping agents of the carbenes.

SUPPL. TERM: dithiolium carbene insertion amide

INDEX TERM: Carbenes (methylene derivatives)
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(dithiolium, insertion reaction of, with benzamide, diphenylacetamide, and succinimide)

INDEX TERM: Amides, reactions
Imides
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(insertion reactions of, with dithiolium carbenes)

INDEX TERM: Insertion reaction
(of dithiolium carbenes with benzamide, diphenylacetamide, and succinimide)

INDEX TERM: 24395-68-4 24395-74-2 53301-48-7 74731-83-2
ROLE: PROC (Process)
(carbene insertion of, into amides and imides)

INDEX TERM: 5152-94-3P 23780-79-2P 24648-13-3P 50708-37-7P
74731-84-3P 74731-85-4P 74731-86-5P 74731-87-6P
103214-86-4P 103214-87-5P 103214-88-6P 103214-89-7P
103214-90-0P 103214-91-1P 103214-92-2P 103214-93-3P
103214-94-4P **103214-95-5P 103214-96-6P**
103214-97-7P
ROLE: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)

INDEX TERM: 23780-83-8 24396-11-0 32283-21-9 50708-36-6
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with caprolactam)

INDEX TERM: 37912-62-2 103214-98-8
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with diphenyldithiolium perchlorate)

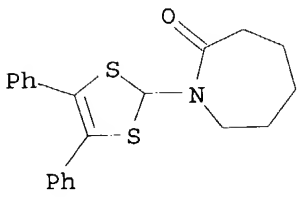
INDEX TERM: 103-84-4 123-56-8 613-93-4
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with dithiolium carbenes)

INDEX TERM: 105-60-2, reactions
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with methoxydithioles in presence of trichloroacetic acid and dithiolium perchlorates)

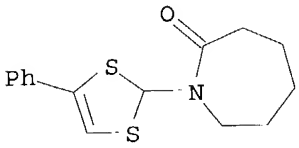
IT **103214-95-5P 103214-96-6P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)

RN 103214-95-5 HCAPLUS

CN 2H-Azepin-2-one, 1-(4,5-diphenyl-1,3-dithiol-2-yl)hexahydro- (9CI) (CA INDEX NAME)



RN 103214-96-6 HCAPLUS
CN 2H-Azepin-2-one, hexahydro-1-(4-phenyl-1,3-dithiol-2-yl)- (9CI) (CA INDEX NAME)



=> d ibib abs ed hitstr 17
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In a multifile environment, a format can only be used if it is valid
in at least one of the files. Refer to file specific help messages
or the STNGUIDE file for information on formats available in
individual files.
REENTER DISPLAY FORMAT FOR ALL FILES (FILEDEFAULT):ibib abs hitstr

L52 ANSWER 17 OF 27 USPATFULL on STN

ACCESSION NUMBER:	2003:238768 USPATFULL
TITLE:	Pyrroloazepine derivatives
INVENTOR(S):	Mizuno, Akira, Kyoto-shi, JAPAN Shibata, Makoto, Ashikaga-shi, JAPAN Iwamori, Tomoe, Ibaraki-shi, JAPAN Shimamoto, Tetsuo, Suita-shi, JAPAN Nakanishi, Kyoko, Ibaraki-shi, JAPAN Inomata, Norio, Minoo-shi, JAPAN
PATENT ASSIGNEE(S):	SUNTORY LIMITED, Osaka-shi, JAPAN (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003166926	A1	20030904
	US 6713634	B2	20040330
APPLICATION INFO.:	US 2002-188234	A1	20020703 (10)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2001-801816, filed on 9 Mar 2001, GRANTED, Pat. No. US 6489473 Continuation of Ser. No. US 1999-312713, filed on 17 May 1999, GRANTED, Pat. No. US 6258805 Continuation of Ser. No. US 1997-875495, filed on 21 Aug 1997, GRANTED, Pat. No. US 5962448 A 371 of International Ser. No. WO 1996-JP3522, filed on 2 Dec 1996, UNKNOWN

	NUMBER	DATE
PRIORITY INFORMATION:	JP 1995-335714	19951201
	JP 1996-46928	19960209
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	OBLON SPIVAK MCCLELLAND MAIER & NEUSTADT PC, FOURTH FLOOR, 1755 JEFFERSON DAVIS HIGHWAY, ARLINGTON, VA, 22202	
NUMBER OF CLAIMS:	39	
EXEMPLARY CLAIM:	1	
LINE COUNT:	4287	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method of effecting serotonin-2-receptor antagonism in a mammal in need thereof, which includes administering to the mammal an effective amount of the compound of the formula (I), or a pharmaceutically acceptable salt thereof: ##STR1##

wherein ring P, the dashed line, A, Y, Z.sub.1 and Z.sub.2 are defined herein.

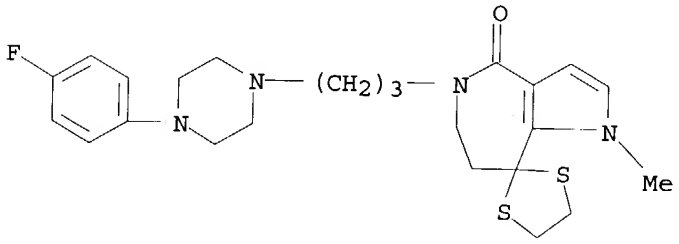
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

IT **191592-05-9P**

(preparation of pyrroloazepine derivs. as serotonin-2 receptor antagonists)

RN 191592-05-9 USPATFULL

CN Spiro[1,3-dithiolane-2,8'(1'H)-pyrrolo[3,2-c]azepin]-4'(5'H)-one, 5'-[3-[4-(4-fluorophenyl)-1-piperazinyl]propyl]-6',7'-dihydro-1'-methyl- (9CI) (CA INDEX NAME)



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L52 ANSWER 18 OF 27 USPATFULL on STN

ACCESSION NUMBER:	2002:141528 USPATFULL
TITLE:	Pyrroloazepine derivatives
INVENTOR(S):	Mizuno, Akira, Kyoto-shi, JAPAN Shibata, Makoto, Ashikaga-shi, JAPAN Iwamori, Tomoe, Ibaraki-shi, JAPAN Shimamoto, Tetsuo, Suita-shi, JAPAN Nakanishi, Kyoko, Ibaraki-shi, JAPAN Inomata, Norio, Minoo-shi, JAPAN
PATENT ASSIGNEE(S):	SUNTORY LIMITED, Osaka-shi, JAPAN, 530 (non-U.S. corporation)

	NUMBER	KIND	DATE

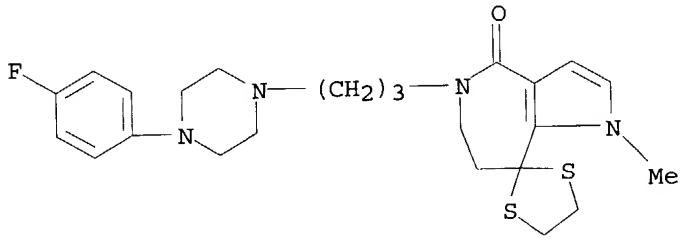
PATENT INFORMATION: US 2002072515 A1 20020613
US 6489473 B2 20021203
APPLICATION INFO.: US 2001-801816 A1 20010309 (9)
RELATED APPLN. INFO.: Continuation of Ser. No. US 1999-312713, filed on 17 May 1999, GRANTED, Pat. No. US 6258805 Continuation of Ser. No. US 1997-875495, filed on 21 Aug 1997, GRANTED, Pat. No. US 5962448 Continuation of Ser. No. WO 1996-JP3522, filed on 2 Dec 1996, UNKNOWN

	NUMBER	DATE
PRIORITY INFORMATION:	JP 1995-335714	19951201
	JP 1996-46928	19960209

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: OBLON SPIVAK MCCLELLAND MAIER & NEUSTADT PC, FOURTH FLOOR, 1755 JEFFERSON DAVIS HIGHWAY, ARLINGTON, VA, 22202
NUMBER OF CLAIMS: 39
EXEMPLARY CLAIM: 1
LINE COUNT: 4156
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A method of effecting serotonin-2-receptor antagonism in a mammal in need thereof, which entails administering to the mammal an effective amount of a compound of the formula (I), or a pharmaceutically acceptable salt thereof: ##STR1##

wherein ring P, the dashed line, Z.sub.1, Z.sub.2, A and Y are as defined herein.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **191592-05-9P**
(preparation of pyrroloazepine derivs. as serotonin-2 receptor antagonists)
RN 191592-05-9 USPATFULL
CN Spiro[1,3-dithiolane-2,8'(1'H)-pyrrolo[3,2-c]azepin]-4'(5'H)-one, 5'-[3-[4-(4-fluorophenyl)-1-piperazinyl]propyl]-6',7'-dihydro-1'-methyl- (9CI) (CA INDEX NAME)



L52 ANSWER 19 OF 27 USPATFULL on STN
ACCESSION NUMBER: 1999:121350 USPATFULL
TITLE: Pyrroloazepine derivatives
INVENTOR(S): Mizuno, Akira, Kyoto, Japan
Shibata, Makoto, Ashikaga, Japan
Iwamori, Tomoe, Ibaraki, Japan
Shimamoto, Tetsuo, Suita, Japan
Nakanishi, Kyoko, Ibaraki, Japan
Inomata, Norio, Minoo, Japan

PATENT ASSIGNEE(S): Suntory Limited, Osaka, Japan (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5962448		19991005	
	WO 9720845		19970612	
APPLICATION INFO.:	US 1997-875495		19970821	(8)
	WO 1996-JP3522		19961202	
			19970821	PCT 371 date
			19970821	PCT 102(e) date

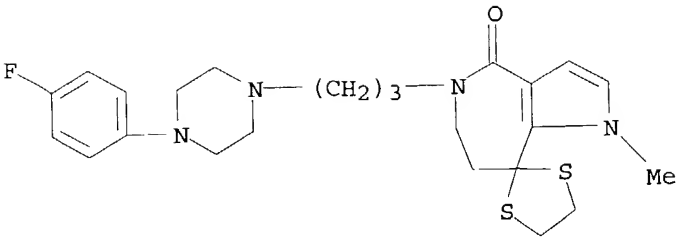
	NUMBER	DATE
PRIORITY INFORMATION:	JP 1995-335714	19951201
	JP 1996-46928	19960209

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Shah, Mukund J.
ASSISTANT EXAMINER: Kifle, Bruck
LEGAL REPRESENTATIVE: Oblon, Spivak, McClelland, Maier & Neustadt, P.C.
NUMBER OF CLAIMS: 31
EXEMPLARY CLAIM: 1
LINE COUNT: 4644
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A pyrroloazepine compound having the following formula (I): wherein

the ring P represented by ##STR1## is a pyrrole ring having the following structure: ##STR2## wherein R.sub.1 represents C.sub.1 -C.sub.8 alkyl, C.sub.3 -C.sub.8 cycloalkyl, C.sub.4 -C.sub.8 cycloalkyl-alkyl, C.sub.6 -C.sub.14 aryl or C.sub.7 -C.sub.22 aralkyl, which are optionally substituted; and R.sub.2 represents H or C.sub.1 -C.sub.8 alkyl, which is optionally substituted; the dashed line indicates the presence or absence of a bond; and, when the bond is present, Z.sub.2 is not present and Z.sub.1 represents H, but, when the bond is absent, Z.sub.1 and Z.sub.2 are both H; Z.sub.1 represents H and Z.sub.2 represents a group OR.sub.3, in which R.sub.3 represents H, C.sub.1 -C.sub.8 alkyl, or C.sub.7 -C.sub.22 aralkyl, which are optionally substituted; Z.sub.1 and Z.sub.2 both represent groups SR.sub.4, in which R.sub.4 represents C.sub.1 -C.sub.8 alkyl or C.sub.7 -C.sub.22 aralkyl, which are optionally substituted; or Z.sub.1 and Z.sub.2 are combined together to represent O, a group NOR.sub.5, in which R.sub.5 represents H, or C.sub.1 -C.sub.8 alkyl or C.sub.2 -C.sub.3 alkylenedithio, which are optionally substituted; A represents alkylene, alkenylene or alkynylene; and Y represents a group in which W is CH, C.dbd. or N, m is for 0 or 1, n is for 1, 2 or 3, G is O, S, C.dbd.O, sulfinyl, sulfonyl, alkylene, alkenylene or acetal; E.sub.1 and E.sub.2 is H or C.sub.1 -C.sub.8 alkyl; and D represents an aromatic hydrocarbon or an aromatic heterocyclic ring. The compound (I) has strong serotonin-2 receptor antagonistic action and low toxicity and less side effects, and is therapeutically useful in the treatment of circulatory diseases and/or conditions related thereto.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **191592-05-9P**
(preparation of pyrroloazepine derivs. as serotonin-2 receptor antagonists)
RN 191592-05-9 USPATFULL
CN Spiro[1,3-dithiolane-2,8'(1'H)-pyrrolo[3,2-c]azepin]-4'(5'H)-one, 5'-[3-[4-(4-fluorophenyl)-1-piperazinyl]propyl]-6',7'-dihydro-1'-methyl- (9CI) (CA INDEX NAME)



L52 ANSWER 20 OF 27 USPATFULL on STN
ACCESSION NUMBER: 1998:25360 USPATFULL
TITLE: Benzo-fused lactams promote release of growth hormone
INVENTOR(S): Schoen, William R., Edison, NJ, United States
Wyvratt, Matthew J., Mountainside, NJ, United States
PATENT ASSIGNEE(S): Merck & Co., Inc., Rahway, NJ, United States (U.S. corporation)

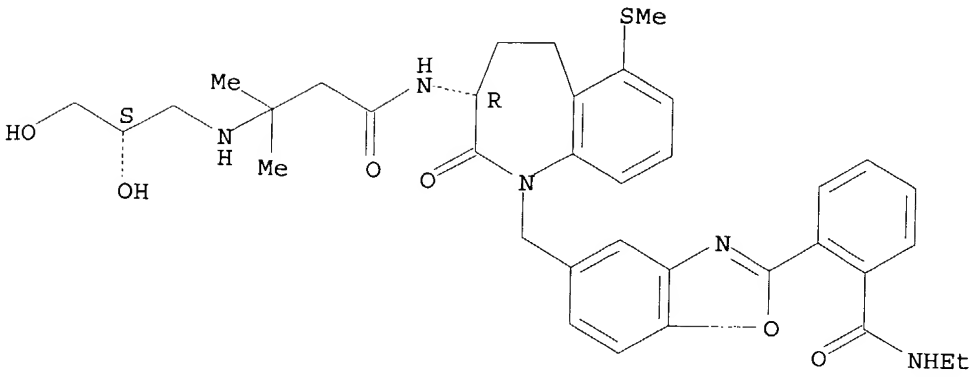
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5726307		19980310
APPLICATION INFO.:	US 1994-356935		19941215 (8)

RELATED APPLN. INFO.: Division of Ser. No. US 1992-961008, filed on 14 Oct 1992, now patented, Pat. No. US 5374721, issued on 20 Dec 1994
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Bond, Robert T.
LEGAL REPRESENTATIVE: Thies, J. Eric, Rose, David L.
NUMBER OF CLAIMS: 6
EXEMPLARY CLAIM: 1
LINE COUNT: 2191
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB There are disclosed certain novel compounds identified as benzo-fused lactams which promote the release of growth hormone in humans and animals. This property can be utilized to promote the growth of food animals to render the production of edible meat products more efficient, and in humans, to increase the stature of those afflicted with a lack of a normal secretion of natural growth hormone. Growth promoting compositions containing such benzo-fused lactams as the active ingredient thereof are also disclosed.

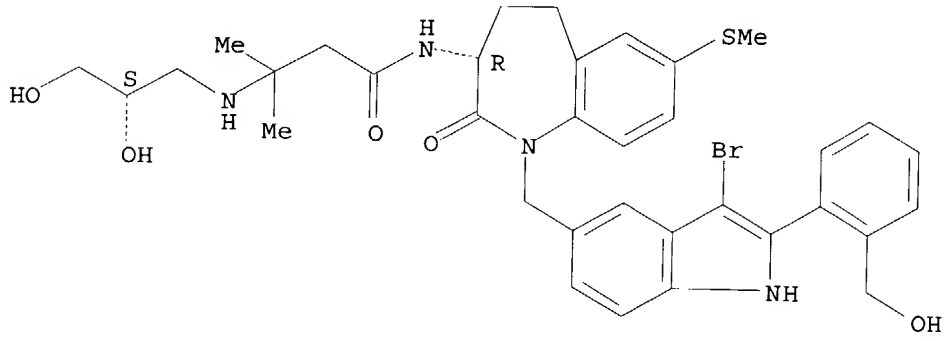
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **167822-74-4P 167822-97-1P**
(preparation of N-(N-heterocyclylbenzazepinyl)aminoalkanamides as growth hormone release promoters)
RN 167822-74-4 USPATFULL
CN Benzamide, 2-[5-[[3-[[3-[(2,3-dihydroxypropyl)amino]-3-methyl-1-oxobutyl]amino]-2,3,4,5-tetrahydro-6-(methylthio)-2-oxo-1H-1-benzazepin-1-yl]methyl]-2-benzoxazolyl]-N-ethyl-, [S-(R*,S*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 167822-97-1 USPATFULL
CN Butanamide, N-[1-[[3-bromo-2-[2-(hydroxymethyl)phenyl]-1H-indol-5-yl]methyl]-2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-3-[(2,3-dihydroxypropyl)amino]-3-methyl-, [S-(R*,S*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L52 ANSWER 21 OF 27 USPATFULL on STN
ACCESSION NUMBER: 96:72979 USPATFULL
TITLE: Benzo-Fused Lactams promote release of growth hormone
INVENTOR(S): Bochis, Richard J., East Brunswick, NJ, United States
Hodges, Paul J., Brick, NJ, United States
Schoen, William R., Edison, NJ, United States
Wyvratt, Jr., Matthew J., Mountainside, NJ, United States
PATENT ASSIGNEE(S): Merck & Co., Inc., Rahway, NJ, United States (U.S. corporation)

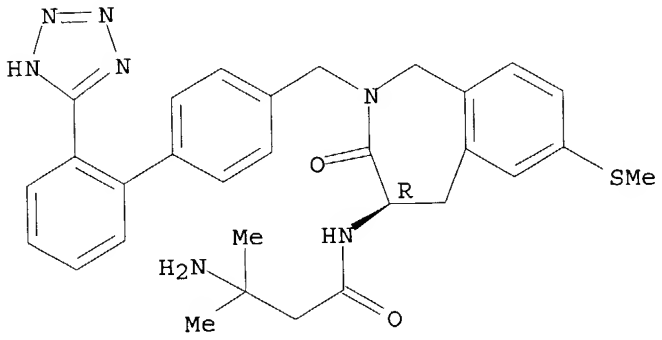
	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5545735		19960813	
APPLICATION INFO.:	US 1993-132074		19931004	(8)
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	Granted			
PRIMARY EXAMINER:	Ford, John M.			
LEGAL REPRESENTATIVE:	Thies, Eric J., Rose, David L.			
NUMBER OF CLAIMS:	6			
EXEMPLARY CLAIM:	1			

searched by D. Arnold 571-272-2532

LINE COUNT: 3239
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB There are disclosed certain novel compounds identified as benzo-fused lactams which promote the release of growth hormone in humans and animals. This property can be utilized to promote the growth of food animals to render the production of edible meat products more efficient, and in humans, to increase the stature of those afflicted with a lack of a normal secretion of natural growth hormone. Growth promoting compositions containing such benzo-fused lactams as the active ingredient thereof are also disclosed.

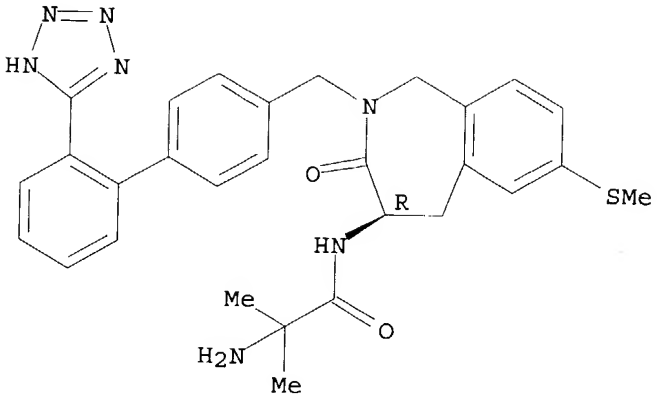
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **168057-13-4P 168057-14-5P 168057-15-6P**
168057-16-7P 168057-25-8P 168057-26-9P
168057-27-0P 168057-37-2P 168057-45-2P
168057-46-3P 168057-47-4P 168057-55-4P
168057-61-2P 168057-67-8P 168057-69-0P
168057-72-5P 168057-78-1P 168057-84-9P
168057-88-3P 168057-92-9P 168057-96-3P
168058-00-2P 168058-04-6P
(preparation of N-(benzazepinonyl)alkanamides as growth hormone release promoters)
RN 168057-13-4 USPATFULL
CN Butanamide, 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-7-(methylthio)-3-oxo-2-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-2-benzazepin-4-yl]-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



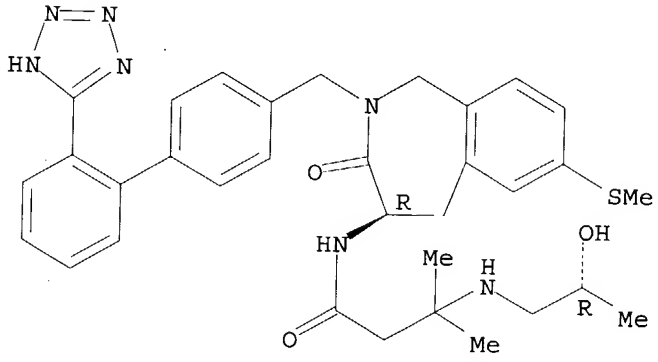
RN 168057-14-5 USPATFULL
CN Propanamide, 2-amino-2-methyl-N-[2,3,4,5-tetrahydro-7-(methylthio)-3-oxo-2-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-2-benzazepin-4-yl]-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



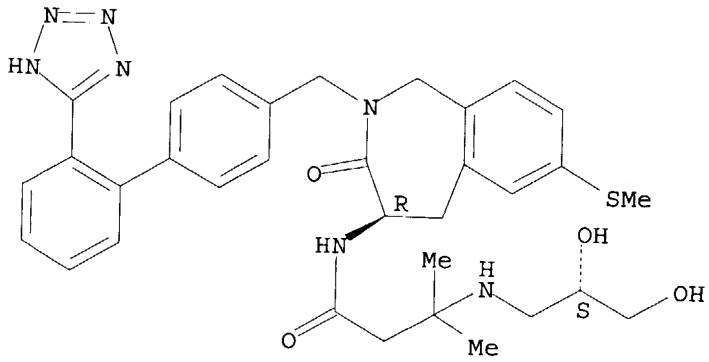
RN 168057-15-6 USPATFULL
CN Butanamide, 3-[(2-hydroxypropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-7-(methylthio)-3-oxo-2-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-2-benzazepin-4-yl]-, [R-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 168057-16-7 USPATFULL
CN Butanamide, 3-[(2,3-dihydroxypropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-7-(methylthio)-3-oxo-2-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-2-benzazepin-4-yl]-, [S-(R*,S*)]- (9CI) (CA INDEX NAME)

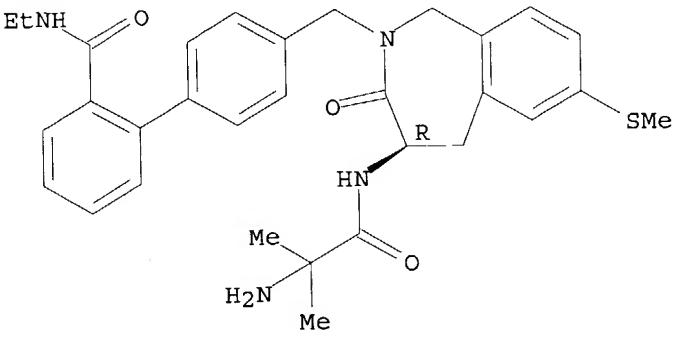
Absolute stereochemistry.



RN 168057-25-8 USPATFULL

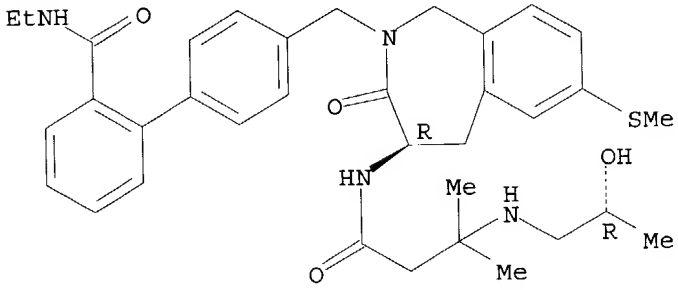
CN [1,1'-Biphenyl]-2-carboxamide, 4'-[[4-[(2-amino-2-methyl-1-oxopropyl)amino]-1,3,4,5-tetrahydro-7-(methylthio)-3-oxo-2H-2-benzazepin-2-yl]methyl]-N-ethyl-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



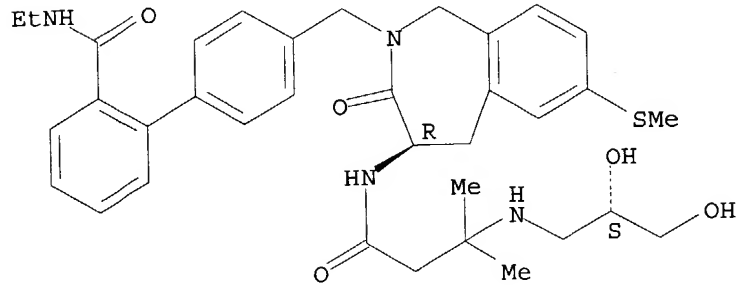
RN 168057-26-9 USPATFULL
CN [1,1'-Biphenyl]-2-carboxamide, N-ethyl-4'-[[1,3,4,5-tetrahydro-4-[[3-[(2-hydroxypropyl)amino]-3-methyl-1-oxobutyl]amino]-7-(methylthio)-3-oxo-2H-2-benzazepin-2-yl]methyl]-, [R-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 168057-27-0 USPATFULL
CN [1,1'-Biphenyl]-2-carboxamide, 4'-[[4-[[3-[(2,3-dihydroxypropyl)amino]-3-methyl-1-oxobutyl]amino]-1,3,4,5-tetrahydro-7-(methylthio)-3-oxo-2H-2-benzazepin-2-yl]methyl]-N-ethyl-, [S-(R*,S*)]- (9CI) (CA INDEX NAME)

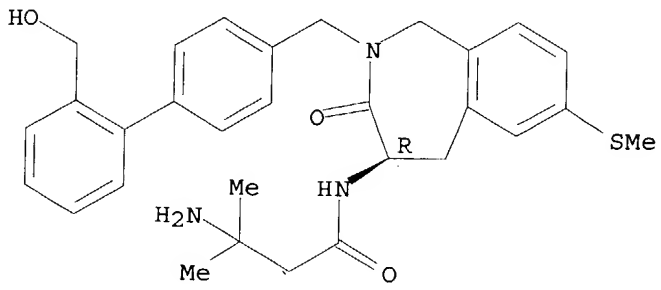
Absolute stereochemistry.



RN 168057-37-2 USPATFULL
CN Butanamide, 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-[[2'-

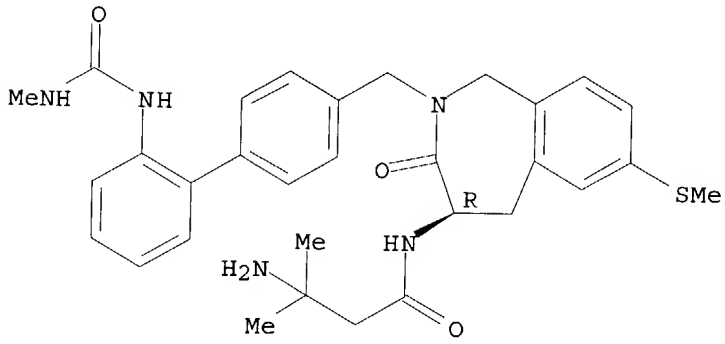
(hydroxymethyl)[1,1'-biphenyl]-4-yl]methyl]-7-(methylthio)-3-oxo-1H-2-benzazepin-4-yl]-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



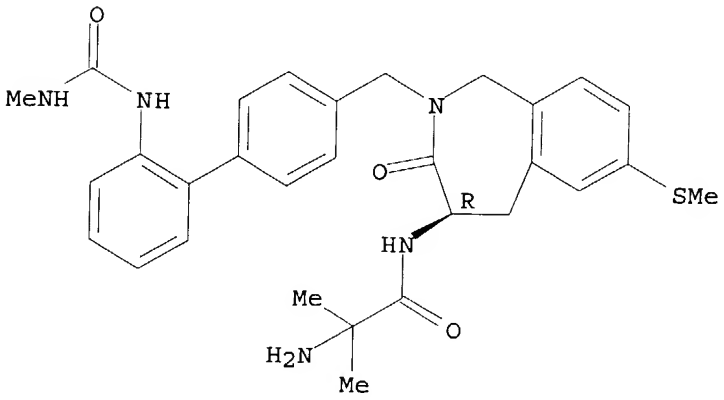
RN 168057-45-2 USPATFULL
CN Butanamide, 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-[[2'-[[(methylamino)carbonyl]amino][1,1'-biphenyl]-4-yl]methyl]-7-(methylthio)-3-oxo-1H-2-benzazepin-4-yl]-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



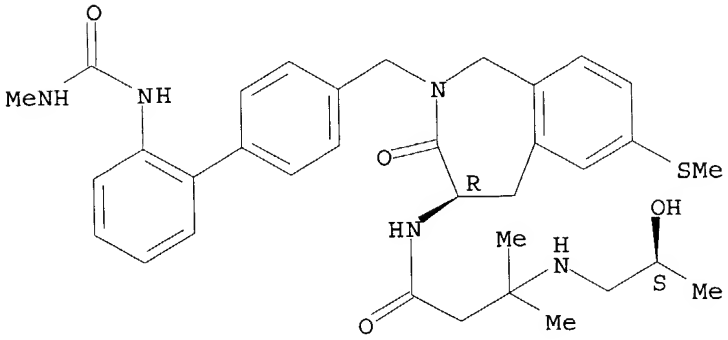
RN 168057-46-3 USPATFULL
CN Propanamide, 2-amino-2-methyl-N-[2,3,4,5-tetrahydro-2-[[2'-[[(methylamino)carbonyl]amino][1,1'-biphenyl]-4-yl]methyl]-7-(methylthio)-3-oxo-1H-2-benzazepin-4-yl]-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



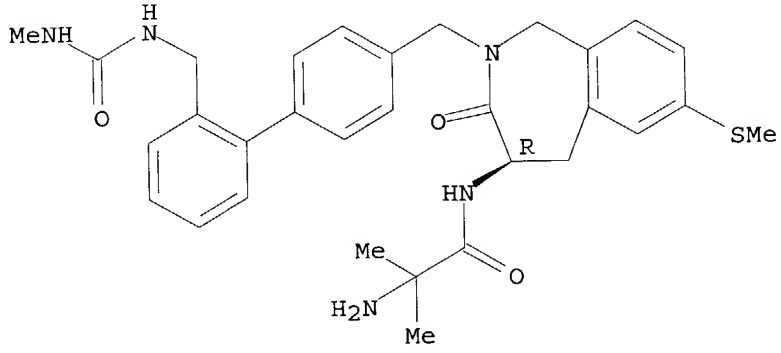
RN 168057-47-4 USPATFULL
CN Butanamide, 3-[(2-hydroxypropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-[[2'-[[(methylamino)carbonyl]amino][1,1'-biphenyl]-4-yl]methyl]-7-(methylthio)-3-oxo-1H-2-benzazepin-4-yl]-, [S-(R*,S*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



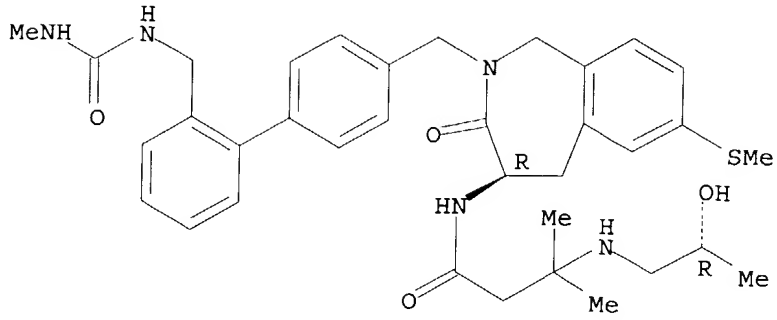
RN 168057-55-4 USPATFULL
CN Propanamide, 2-amino-2-methyl-N-[2,3,4,5-tetrahydro-2-[[2'-[[[(methylamino)carbonyl]amino]methyl][1,1'-biphenyl]-4-yl]methyl]-7-(methylthio)-3-oxo-1H-2-benzazepin-4-yl]-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



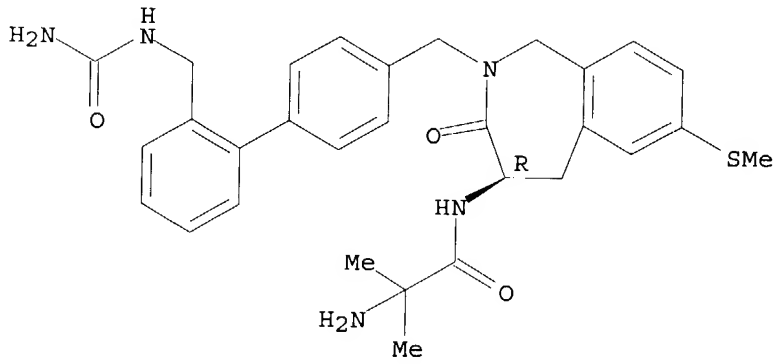
RN 168057-61-2 USPATFULL
CN Butanamide, 3-[(2-hydroxypropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-[[2'-[[[(methylamino)carbonyl]amino]methyl][1,1'-biphenyl]-4-yl]methyl]-7-(methylthio)-3-oxo-1H-2-benzazepin-4-yl]-, [R-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



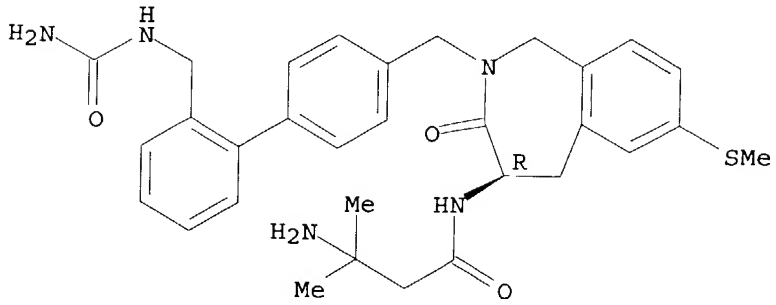
RN 168057-67-8 USPATFULL
CN Propanamide, 2-amino-N-[2-[[2'-[[(aminocarbonyl)amino]methyl][1,1'-biphenyl]-4-yl]methyl]-2,3,4,5-tetrahydro-7-(methylthio)-3-oxo-1H-2-benzazepin-4-yl]-2-methyl-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 168057-69-0 USPATFULL
CN Butanamide, 3-amino-N-[2-[[2'-[[(aminocarbonyl)amino]methyl][1,1'-biphenyl]-4-yl]methyl]-2,3,4,5-tetrahydro-7-(methylthio)-3-oxo-1H-2-benzazepin-4-yl]-3-methyl-, (R)- (9CI) (CA INDEX NAME)

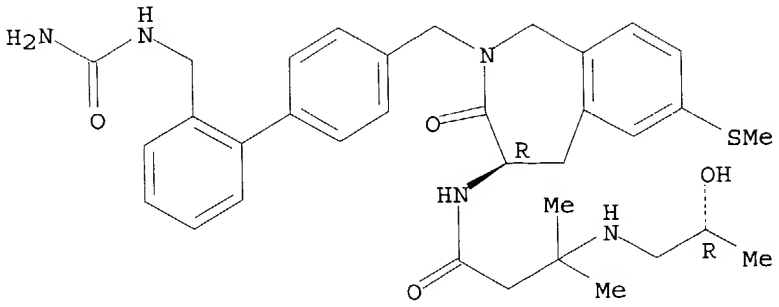
Absolute stereochemistry.



RN 168057-72-5 USPATFULL
CN Butanamide, N-[2-[[2'-[[(aminocarbonyl)amino]methyl][1,1'-biphenyl]-4-yl]methyl]-2,3,4,5-tetrahydro-7-(methylthio)-3-oxo-1H-2-benzazepin-4-yl]-3-[(2-hydroxypropyl)amino]-3-methyl-, [R-(R*,R*)]- (9CI) (CA INDEX

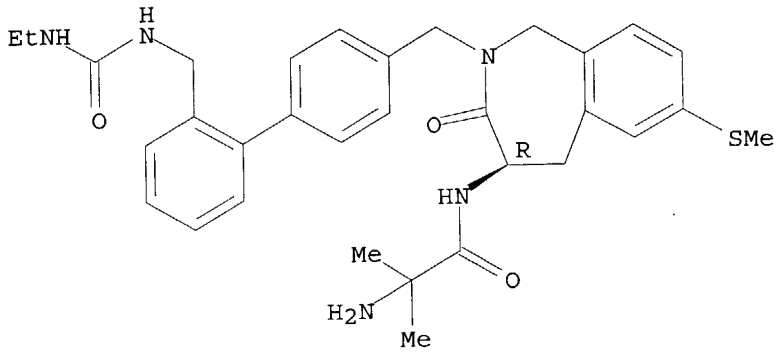
NAME)

Absolute stereochemistry.



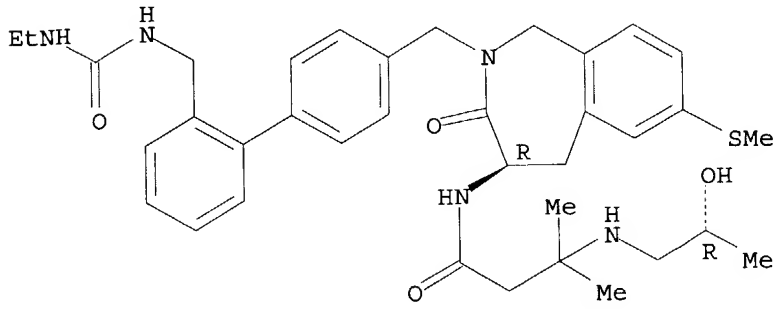
RN 168057-78-1 USPATFULL
CN Propanamide, 2-amino-N-[2-[[2'-[[[(ethylamino)carbonyl]amino]methyl][1,1'-biphenyl]-4-yl]methyl]-2,3,4,5-tetrahydro-7-(methylthio)-3-oxo-1H-2-benzazepin-4-yl]-2-methyl-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



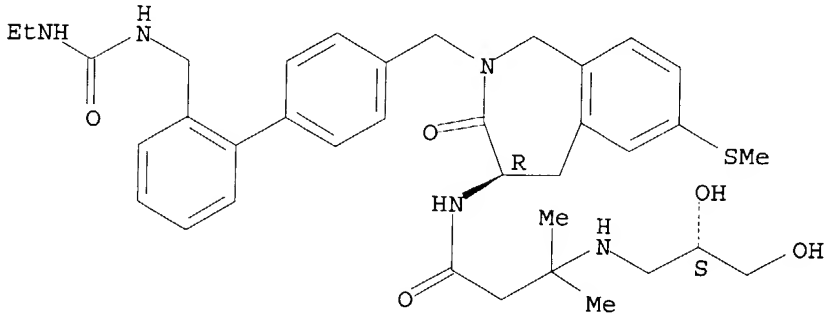
RN 168057-84-9 USPATFULL
CN Butanamide, N-[2-[[2'-[[[(ethylamino)carbonyl]amino]methyl][1,1'-biphenyl]-4-yl]methyl]-2,3,4,5-tetrahydro-7-(methylthio)-3-oxo-1H-2-benzazepin-4-yl]-3-[(2-hydroxypropyl)amino]-3-methyl-, [R-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



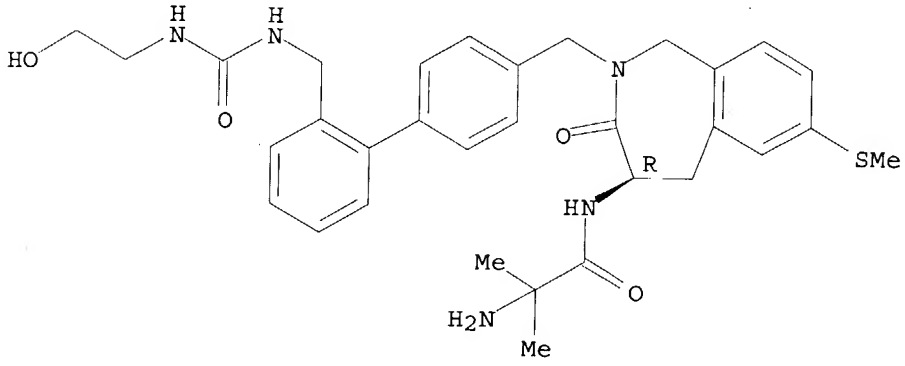
RN 168057-88-3 USPATFULL
CN Butanamide, 3-[(2,3-dihydroxypropyl)amino]-N-[2-[[2'-[[[(ethylamino)carbonyl]amino]methyl][1,1'-biphenyl]-4-yl]methyl]-2,3,4,5-tetrahydro-7-(methylthio)-3-oxo-1H-2-benzazepin-4-yl]-3-methyl-, [S-(R*,S*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



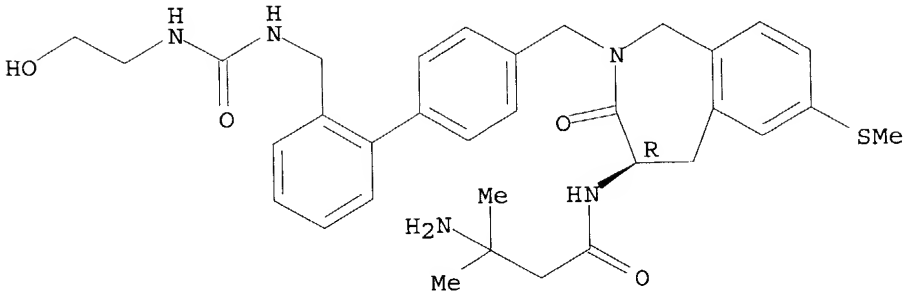
RN 168057-92-9 USPATFULL
CN Propanamamide, 2-amino-2-methyl-N-[2,3,4,5-tetrahydro-2-[[2'-[[[[(2-hydroxyethyl)amino]carbonyl]amino]methyl][1,1'-biphenyl]-4-yl]methyl]-7-(methylthio)-3-oxo-1H-2-benzazepin-4-yl]-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



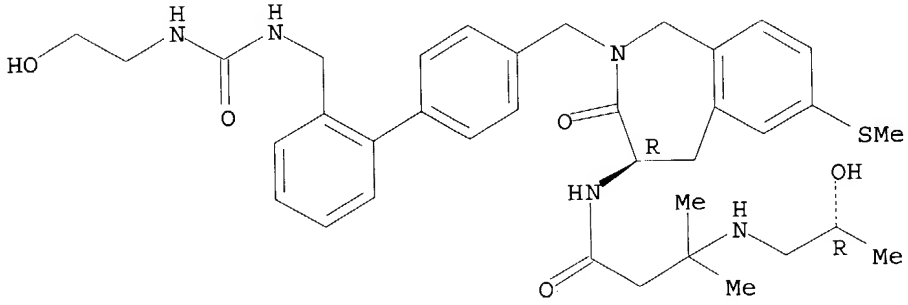
RN 168057-96-3 USPATFULL
CN Butanamide, 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-[[2'-[[[[(2-hydroxyethyl)amino]carbonyl]amino]methyl][1,1'-biphenyl]-4-yl]methyl]-7-(methylthio)-3-oxo-1H-2-benzazepin-4-yl]-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



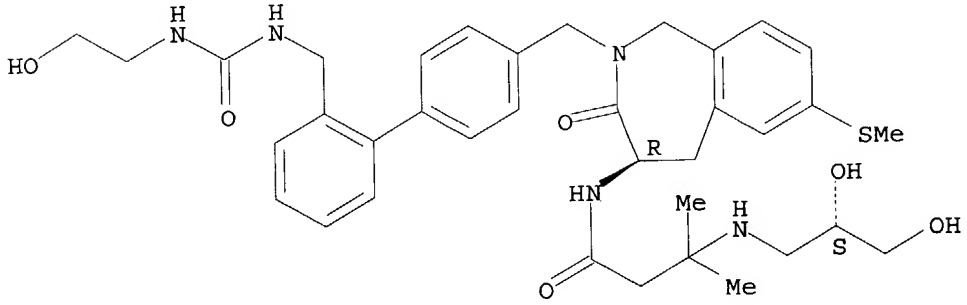
RN 168058-00-2 USPATFULL
CN Butanamide, 3-[(2-hydroxypropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-[[2'-[[[[(2-hydroxyethyl)amino]carbonyl]amino]methyl][1,1'-biphenyl]-4-yl]methyl]-7-(methylthio)-3-oxo-1H-2-benzazepin-4-yl]-, [R-(R*,R*)]-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 168058-04-6 USPATFULL
CN Butanamide, 3-[(2,3-dihydroxypropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-[[2'-[[[[(2-hydroxyethyl)amino]carbonyl]amino]methyl][1,1'-biphenyl]-4-yl]methyl]-7-(methylthio)-3-oxo-1H-2-benzazepin-4-yl]-, [R-(R*,S*)]-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



L52 ANSWER 22 OF 27 USPATFULL on STN
ACCESSION NUMBER: 95:65030 USPATFULL
TITLE: Benzo-fused lactams promote release of growth hormone

INVENTOR(S):	Schoen, William R., Edison, NJ, United States Wyvratt, Jr., Matthew J., Mountainside, NJ, United States
PATENT ASSIGNEE(S):	Merck & Co., Inc., Rahway, NJ, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5434261		19950718
APPLICATION INFO.:	US 1993-97149		19930726 (8)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Bond, Robert T.
LEGAL REPRESENTATIVE:	Thies, J. Eric, Rose, David L.
NUMBER OF CLAIMS:	6
EXEMPLARY CLAIM:	1
LINE COUNT:	2342

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB There are disclosed certain novel compounds identified as benzo-fused lactams which promote the release of growth hormone in humans and animals. This property can be utilized to promote the growth of food animals to render the production of edible meat products more efficient, and in humans, to increase the stature of those afflicted with a lack of a normal secretion of natural growth hormone. Growth promoting compositions containing such benzo-fused lactams as the active ingredient thereof are also disclosed.

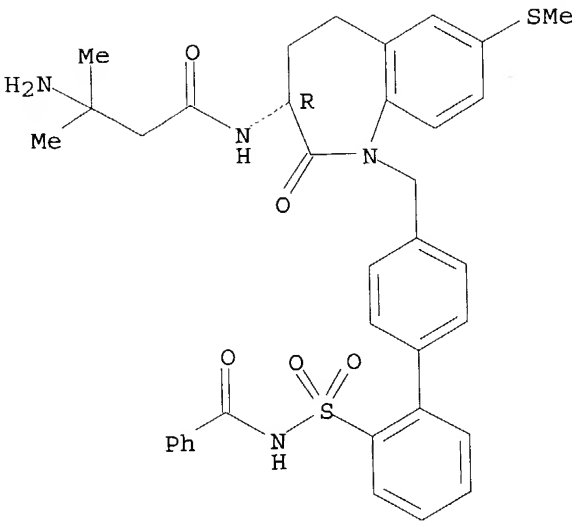
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

IT **169188-22-1P 169188-27-6P 169188-32-3P**
169188-37-8P 169188-42-5P 169188-47-0P
169188-52-7P 169188-57-2P 169188-61-8P
169188-66-3P 169188-71-0P 169188-76-5P
169188-80-1P 169188-85-6P 169188-90-3P
169188-95-8P
(preparation of benzo-fused lactams which promote release of growth hormone)

RN 169188-22-1 USPATFULL

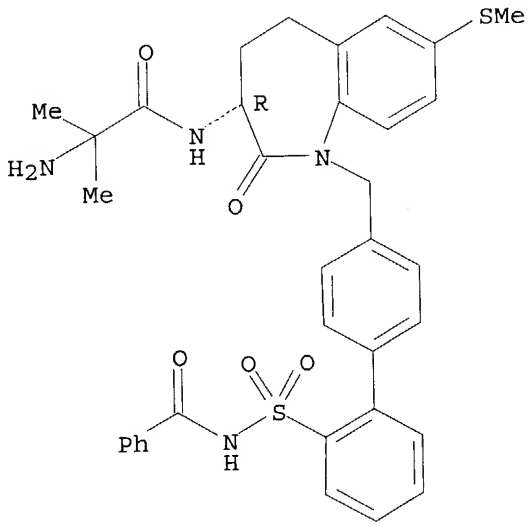
CN Benzamide, N-[[4'-[[3-[(3-amino-3-methyl-1-oxobutyl)amino]-2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1'-biphenyl]-2-yl]sulfonyl]-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



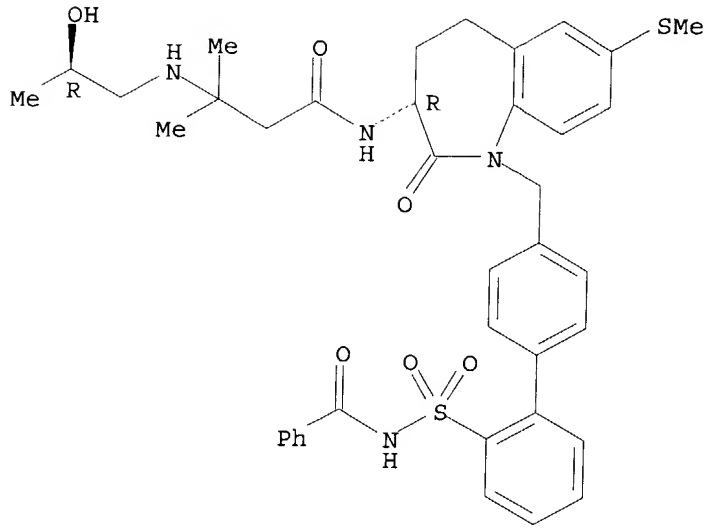
RN 169188-27-6 USPATFULL
CN Benzamide, N-[[4'-[[3-[(2-amino-2-methyl-1-oxopropyl)amino]-2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1'-biphenyl]-2-yl]sulfonyl]-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



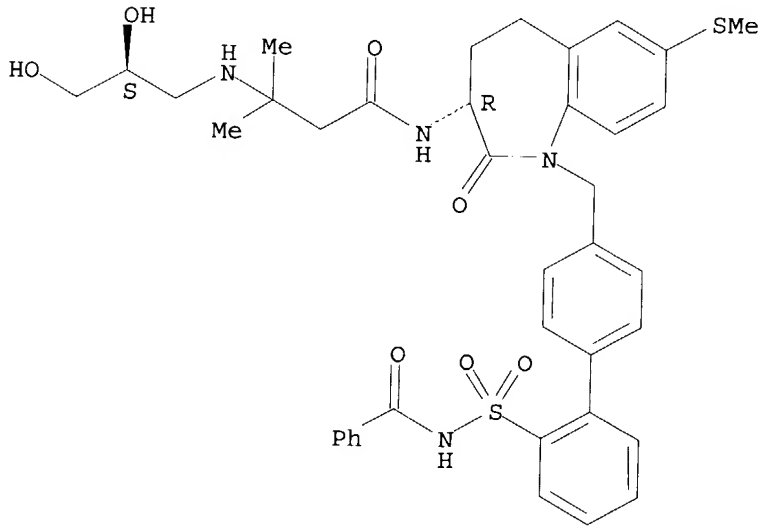
RN 169188-32-3 USPATFULL
CN Benzamide, N-[[4'-[[2,3,4,5-tetrahydro-3-[[3-[(2-hydroxypropyl)amino]-3-methyl-1-oxobutyl]amino]-7-(methylthio)-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1'-biphenyl]-2-yl]sulfonyl]-, [R-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



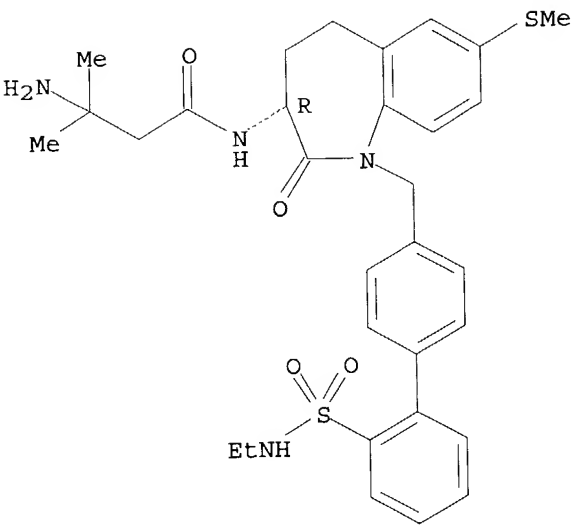
RN 169188-37-8 USPATFULL
CN Benzamide, N-[[4'-[[3-[[3-[(2,3-dihydroxypropyl)amino]-3-methyl-1-oxobutyl]amino]-2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1'-biphenyl]-2-yl]sulfonyl]-, [S-(R*,S*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



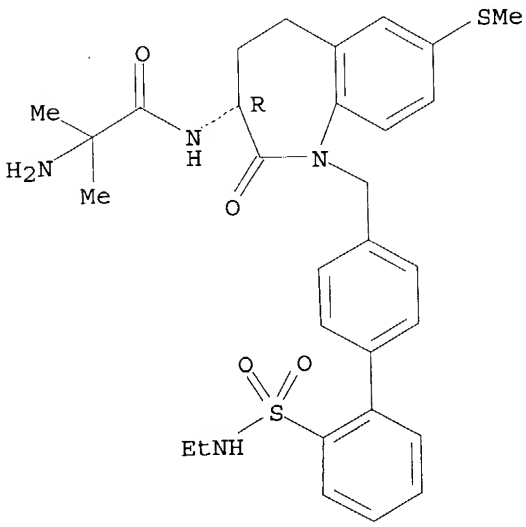
RN 169188-42-5 USPATFULL
CN Butanamide, 3-amino-N-[1-[[2'-[(ethylamino)sulfonyl][1,1'-biphenyl]-4-yl]methyl]-2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-3-methyl-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



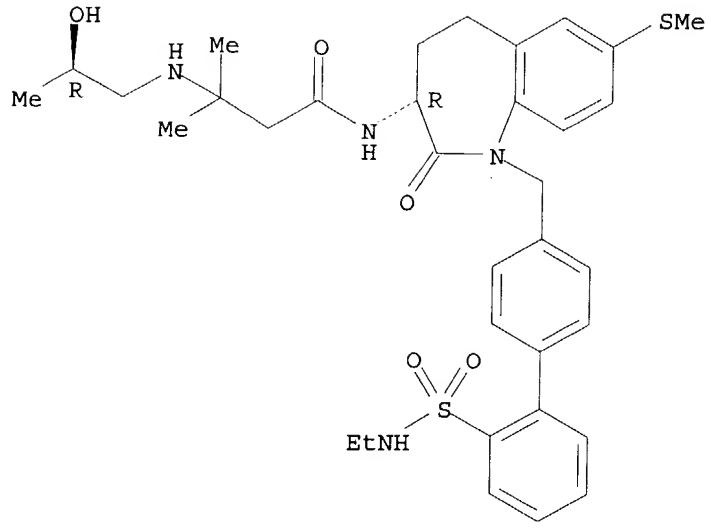
RN 169188-47-0 USPATFULL
CN Propanamide, 2-amino-N-[1-[[2'-[(ethylamino)sulfonyl][1,1'-biphenyl]-4-yl]methyl]-2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-2-methyl-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



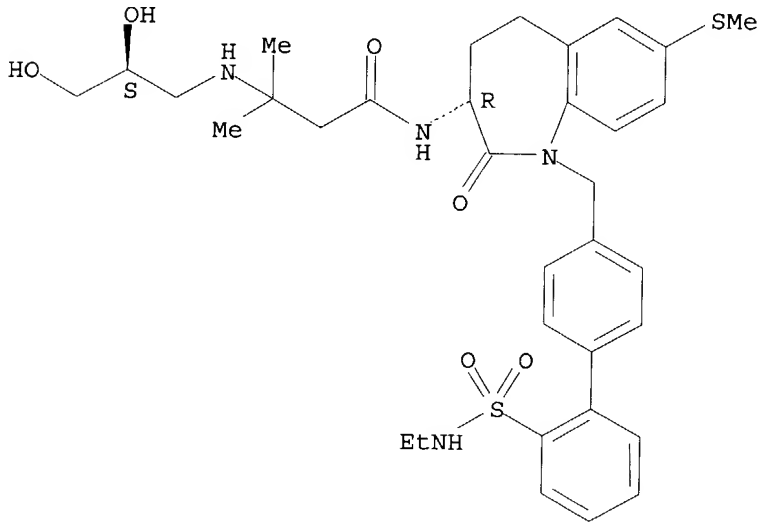
RN 169188-52-7 USPATFULL
CN Butanamide, N-[1-[[2'-[(ethylamino)sulfonyl][1,1'-biphenyl]-4-yl]methyl]-2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-3-[(2-hydroxypropyl)amino]-3-methyl-, [R-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



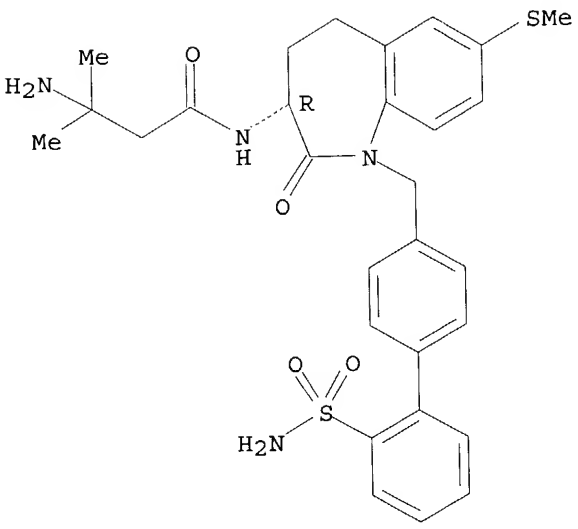
RN 169188-57-2 USPATFULL
CN Butanamide, 3-[(2,3-dihydroxypropyl)amino]-N-[1-[[2'-[(ethylamino)sulfonyl][1,1'-biphenyl]-4-yl]methyl]-2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-3-methyl-, [S-(R*,S*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



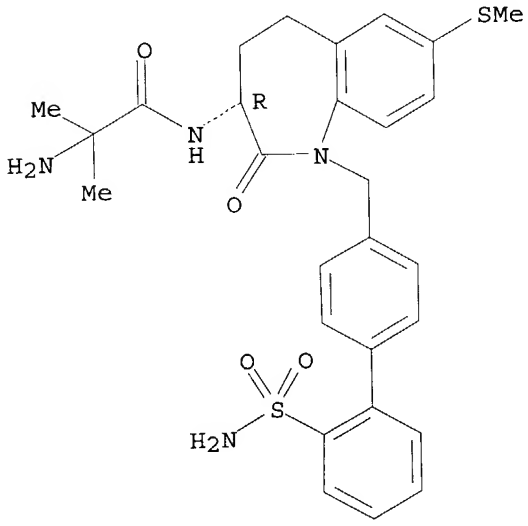
RN 169188-61-8 USPATFULL
CN Butanamide, 3-amino-N-[1-[[2'-(aminosulfonyl)[1,1'-biphenyl]-4-yl]methyl]-2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-3-methyl-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



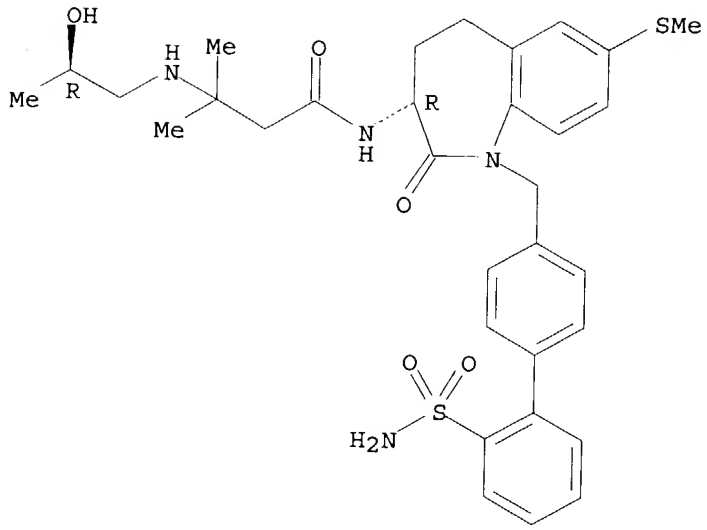
RN 169188-66-3 USPATFULL
CN Propanamide, 2-amino-N-[1-[[2'-(aminosulfonyl)[1,1'-biphenyl]-4-yl]methyl]-2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-2-methyl-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



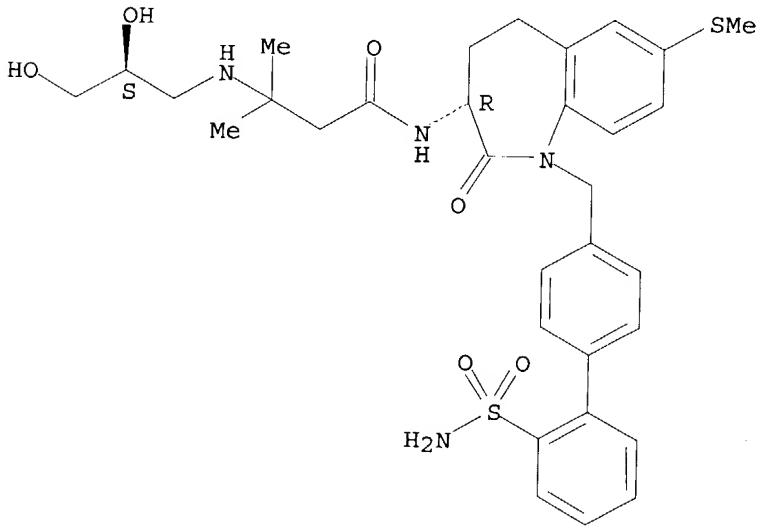
RN 169188-71-0 USPATFULL
CN Butanamide, N-[1-[[2'-(aminosulfonyl)[1,1'-biphenyl]-4-yl]methyl]-2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-3-[(2-hydroxypropyl)amino]-3-methyl-, [R-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



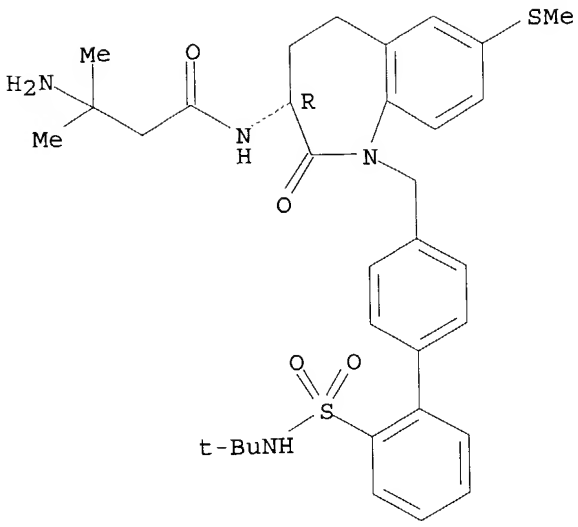
RN 169188-76-5 USPATFULL
CN Butanamide, N-[1-[[2'-(aminosulfonyl)[1,1'-biphenyl]-4-yl]methyl]-2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-3-[(2,3-dihydroxypropyl)amino]-3-methyl-, [S-(R*,S*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



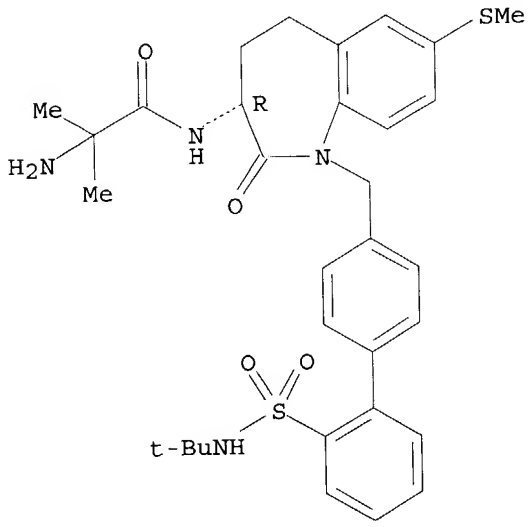
RN 169188-80-1 USPATFULL
CN Butanamide, 3-amino-N-[1-[[2'-[[(1,1-dimethylethyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-3-methyl-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



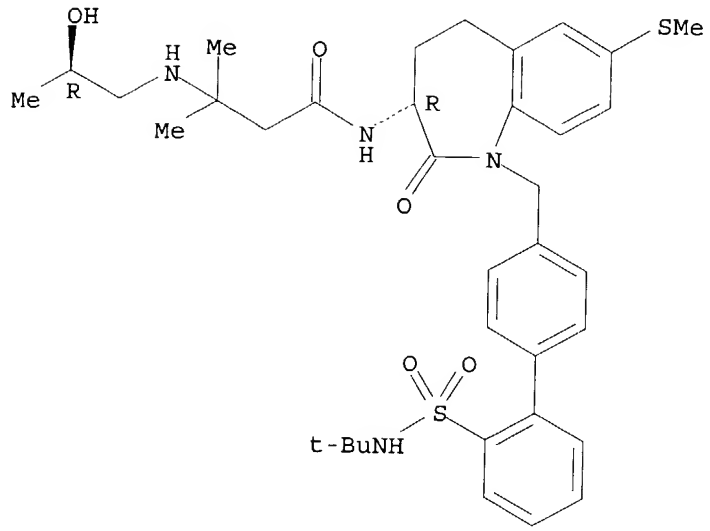
RN 169188-85-6 USPATFULL
CN Propanamide, 2-amino-N-[1-[[2'-[[(1,1-dimethylethyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-2-methyl-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



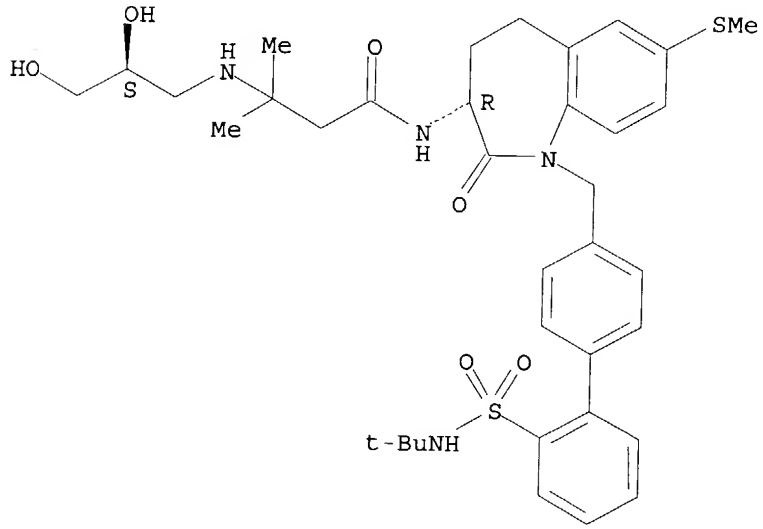
RN 169188-90-3 USPATFULL
CN Butanamide, N-[1-[[2'-[[(1,1-dimethylethyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-3-[(2-hydroxypropyl)amino]-3-methyl-, [R-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 169188-95-8 USPATFULL
CN Butanamide, 3-[(2,3-dihydroxypropyl)amino]-N-[1-[[2'-[[(1,1-dimethylethyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-3-methyl-, [S-(R*,S*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L52 ANSWER 23 OF 27 USPATFULL on STN
ACCESSION NUMBER: 95:60479 USPATFULL
TITLE: Benzo-fused lactams promote release of growth hormone
INVENTOR(S): Schoen, William R., Edison, NJ, United States
Wyvratt, Jr., Matthew J., Mountainside, NJ, United States
Hodges, Paul J., Brick, NJ, United States
PATENT ASSIGNEE(S): Merck & Co., Inc., Rahway, NJ, United States (U.S.

corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5430144		19950704	
APPLICATION INFO.:	US 1993-97146		19930726	(8)
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	Granted			
PRIMARY EXAMINER:	Bond, Robert T.			
LEGAL REPRESENTATIVE:	Thies, J. Eric, Rose, David			
NUMBER OF CLAIMS:	6			
EXEMPLARY CLAIM:	1			
LINE COUNT:	2326			

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB There are disclosed certain novel compounds identified as benzo-fused lactams which promote the release of growth hormone in humans and animals. This property can be utilized to promote the growth of food animals to render the production of edible meat products more efficient, and in humans, to increase the stature of those afflicted with a lack of a normal secretion of natural growth hormone. Growth promoting compositions containing such benzo-fused lactams as the active ingredient thereof are also disclosed.

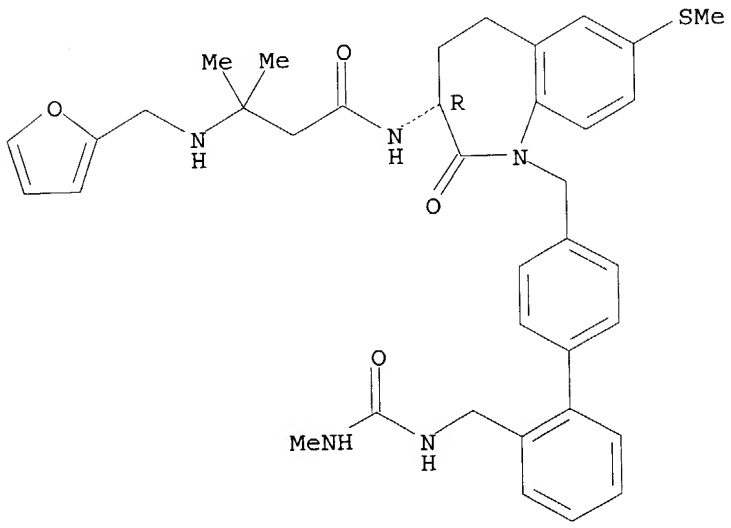
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

IT **169187-36-4P 169187-41-1P 169187-46-6P**
169187-51-3P 169187-56-8P 169187-61-5P
169187-66-0P
(preparation of N-(oxobenzazepinyl)alkanamides as growth hormone release promoters)

RN 169187-36-4 USPATFULL

CN Butanamide, 3-[(2-furanylmethyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-1-[[2'-[[[(methylamino)carbonyl]amino]methyl][1,1'-biphenyl]-4-yl]methyl]-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

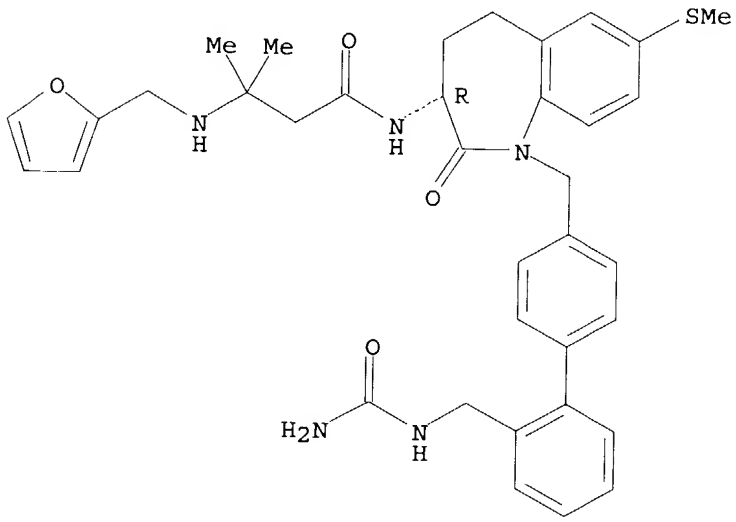


RN 169187-41-1 USPATFULL

CN Butanamide, N-[1-[[2'-[[(aminocarbonyl)amino]methyl][1,1'-biphenyl]-4-yl]methyl]-2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-

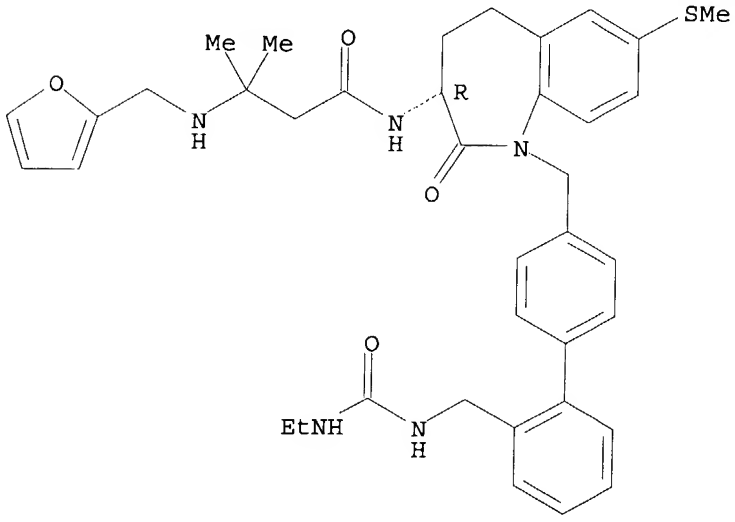
3-[(2-furanylmethyl)amino]-3-methyl-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



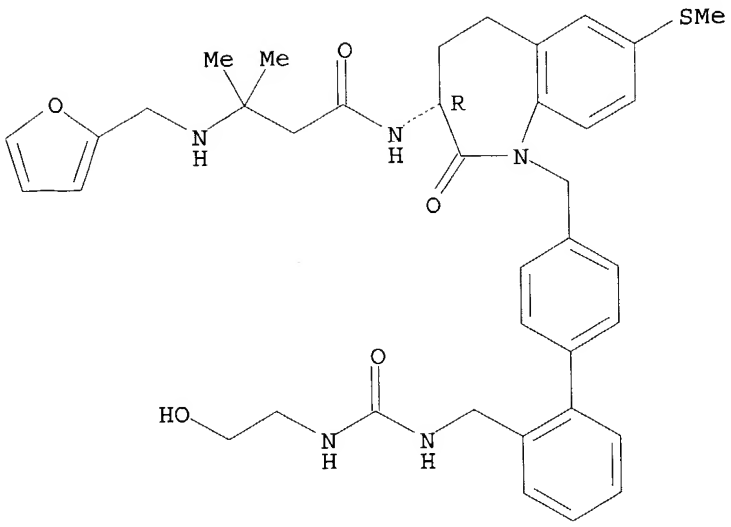
RN 169187-46-6 USPATFULL
CN Butanamide, N-[1-[[2'-[[[(ethylamino)carbonyl]amino]methyl][1,1'-biphenyl]-4-yl]methyl]-2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-3-[(2-furanylmethyl)amino]-3-methyl-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



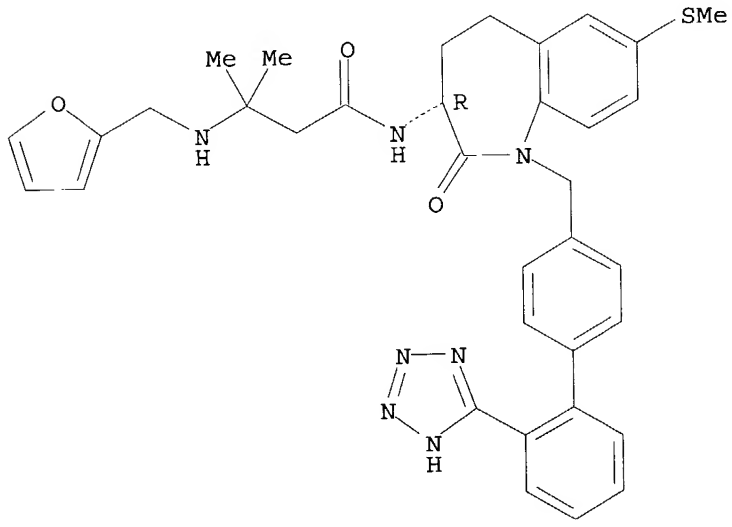
RN 169187-51-3 USPATFULL
CN Butanamide, 3-[(2-furanylmethyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-1-[[2'-[[[[(2-hydroxyethyl)amino]carbonyl]amino]methyl][1,1'-biphenyl]-4-yl]methyl]-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



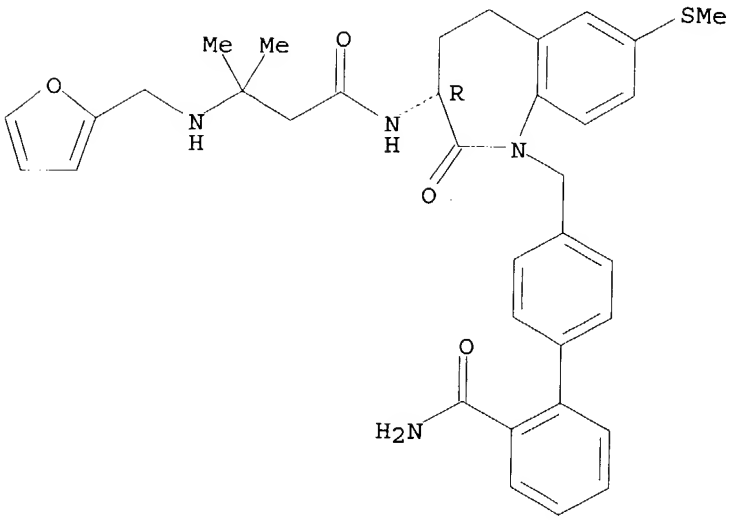
RN 169187-56-8 USPATFULL
CN Butanamide, 3-[(2-furanylmethyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



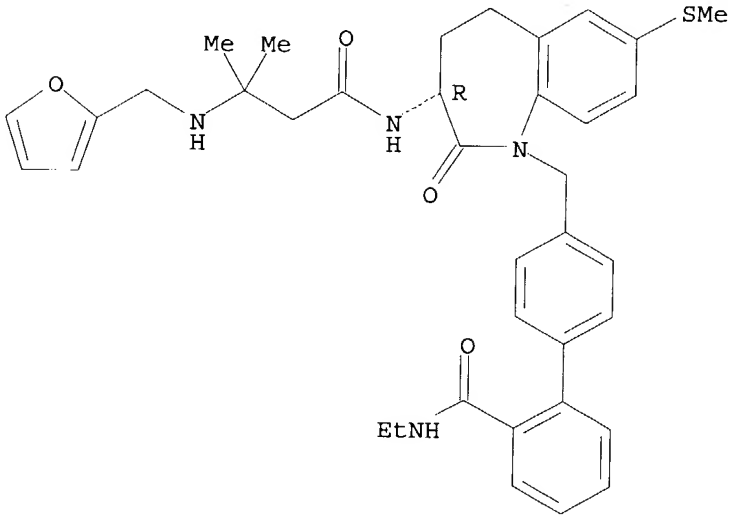
RN 169187-61-5 USPATFULL
CN [1,1'-Biphenyl]-2-carboxamide, 4'-[[3-[[3-[(2-furanylmethyl)amino]-3-methyl-1-oxobutyl]amino]-2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1H-1-benzazepin-1-yl]methyl]-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 169187-66-0 USPATFULL
CN [1,1'-Biphenyl]-2-carboxamide, N-ethyl-4'-[[3-[[3-[(2-furanylmethyl)amino]-3-methyl-1-oxobutyl]amino]-2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1H-1-benzazepin-1-yl]methyl]-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L52 ANSWER 24 OF 27 USPATFULL on STN
ACCESSION NUMBER: 94:110863 USPATFULL
TITLE: Benzo-fused lactams promote release of growth hormone
INVENTOR(S): Schoen, William R., Edison, NJ, United States
Wyvratt, Matthew J., Mountainside, NJ, United States
PATENT ASSIGNEE(S): Merck & Co., Inc., Rahway, NJ, United States (U.S. corporation)

NUMBER KIND DATE

PATENT INFORMATION:	US 5374721	19941220
APPLICATION INFO.:	US 1992-961008	19921014 (7)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	Granted	
PRIMARY EXAMINER:	Bond, Robert T.	
LEGAL REPRESENTATIVE:	Rose, David L., DiPrima, Joseph F.	
NUMBER OF CLAIMS:	6	
EXEMPLARY CLAIM:	1	
LINE COUNT:	2322	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB There are disclosed certain novel compounds identified as benzo-fused lactams which promote the release of growth hormone in humans and animals. This property can be utilized to promote the growth of food animals to render the production of edible meat products more efficient, and in humans, to increase the stature of those afflicted with a lack of a normal secretion of natural growth hormone. Growth promoting compositions containing such benzo-fused lactams as the active ingredient thereof are also disclosed.

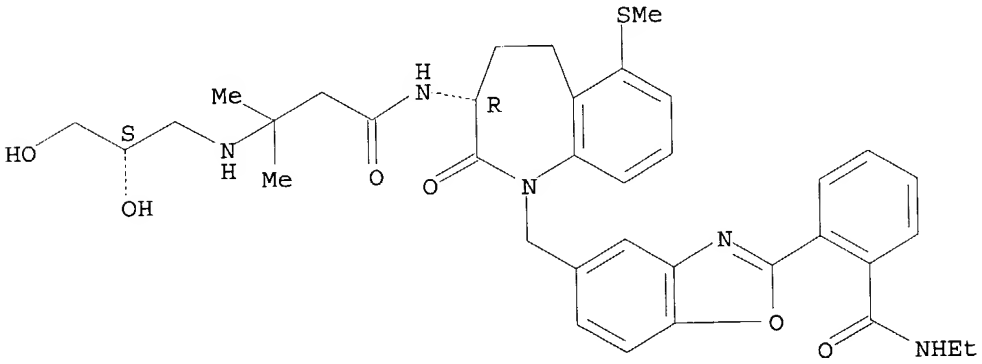
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

IT **167822-74-4P 167822-97-1P**
(preparation of N-(N-heterocyclylbenzazepinyl)aminoalkanamides as growth hormone release promoters)

RN 167822-74-4 USPATFULL

CN Benzamide, 2-[5-[[3-[[3-[(2,3-dihydroxypropyl)amino]-3-methyl-1-oxobutyl]amino]-2,3,4,5-tetrahydro-6-(methylthio)-2-oxo-1H-1-benzazepin-1-yl]methyl]-2-benzoxazolyl]-N-ethyl-, [S-(R*,S*)]- (9CI) (CA INDEX NAME)

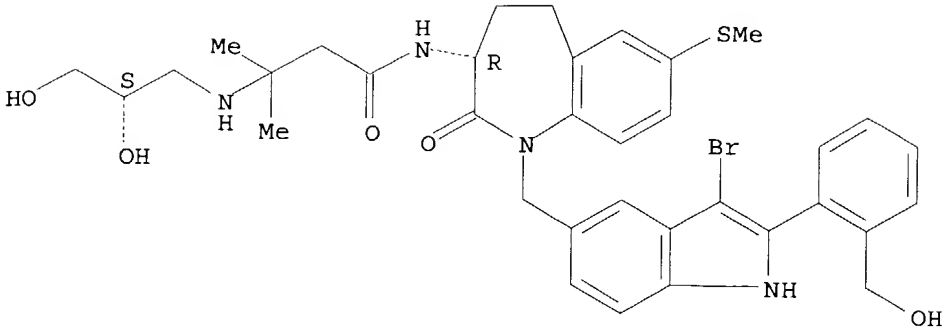
Absolute stereochemistry.



RN 167822-97-1 USPATFULL

CN Butanamide, N-[1-[[3-bromo-2-[2-(hydroxymethyl)phenyl]-1H-indol-5-yl]methyl]-2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-3-[(2,3-dihydroxypropyl)amino]-3-methyl-, [S-(R*,S*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



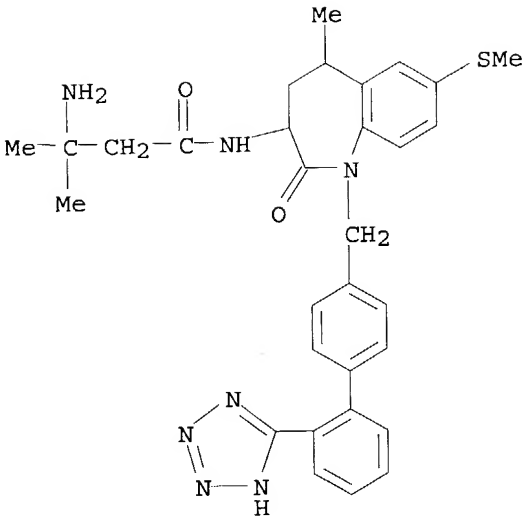
L52 ANSWER 25 OF 27 USPATFULL on STN
ACCESSION NUMBER: 94:46974 USPATFULL
TITLE: N-biphenyl-3-amido substituted benzolactams stimulate growth hormone release
INVENTOR(S): Ok, Hyun O., Edison, NJ, United States
Schoen, William R., Edison, NJ, United States
Wyvratt, Matthew, Mountainside, NJ, United States
PATENT ASSIGNEE(S): Merck & Co., Inc., Rahway, NJ, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5317017		19940531
APPLICATION INFO.:	US 1992-954220		19920930 (7)

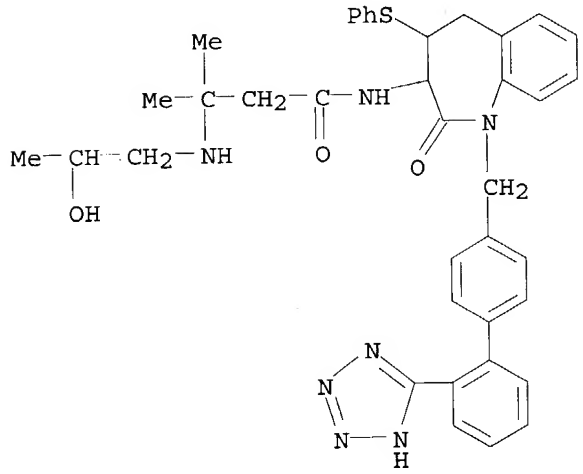
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Higel, Floyd D.
LEGAL REPRESENTATIVE: Rose, David L., DiPrima, Joseph F.
NUMBER OF CLAIMS: 13
EXEMPLARY CLAIM: 1,7
LINE COUNT: 2161
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB There are disclosed certain compounds identified as N-biphenyl-3-amido substituted benzolactams which promote the release of growth hormone in humans and animals. This property can be utilized to promote the growth of food animals to render the production of edible meat products more efficient, and in humans, to increase the stature of those afflicted with a lack of a normal secretion of natural growth hormone. Growth promoting compositions containing such benzolactams as the active ingredient thereof are also disclosed.

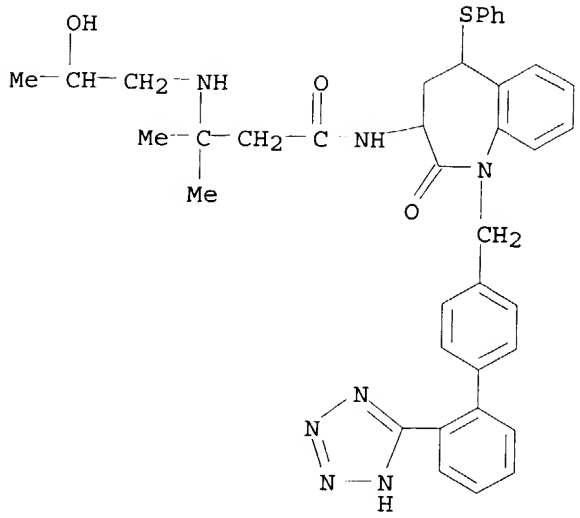
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **158104-10-0 158104-11-1 158104-12-2 158104-21-3 158104-31-5 158104-42-8**
(growth hormone release accelerator)
RN 158104-10-0 USPATFULL
CN Butanamide, 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-5-methyl-7-(methylthio)-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]- (9CI) (CA INDEX NAME)



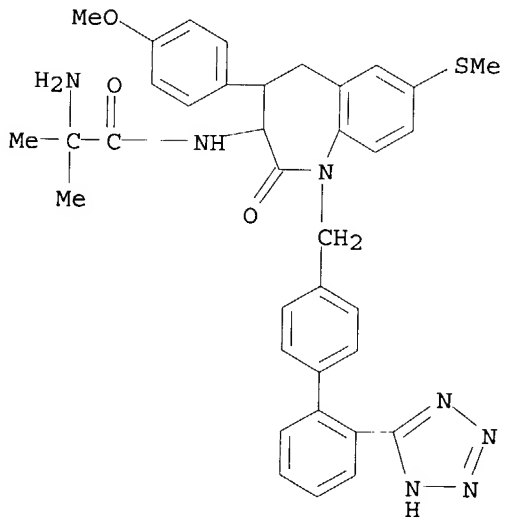
RN 158104-11-1 USPATFULL
CN Butanamide, 3-[(2-hydroxypropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-4-(phenylthio)-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]- (9CI) (CA INDEX NAME)



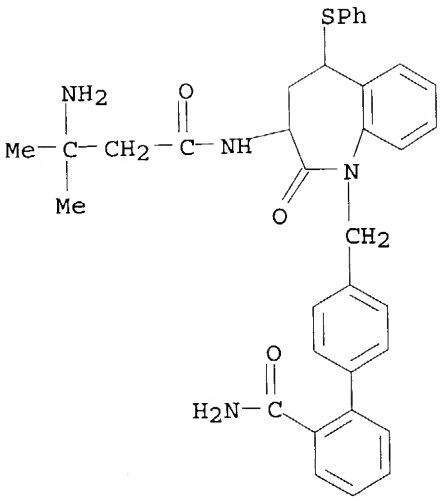
RN 158104-12-2 USPATFULL
CN Butanamide, 3-[(2-hydroxypropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-5-(phenylthio)-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]- (9CI) (CA INDEX NAME)



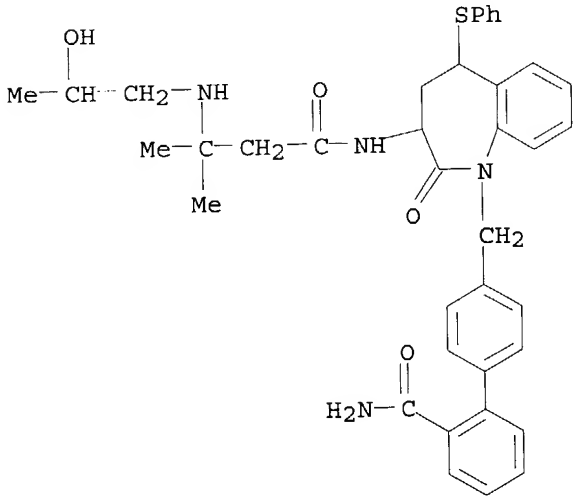
RN 158104-21-3 USPATFULL
CN Propanamide, 2-amino-2-methyl-N-[2,3,4,5-tetrahydro-4-(4-methoxyphenyl)-7-(methylthio)-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]- (9CI) (CA INDEX NAME)



RN 158104-31-5 USPATFULL
CN [1,1'-Biphenyl]-2-carboxamide, 4'-[[3-[(3-amino-3-methyl-1-oxobutyl)amino]-2,3,4,5-tetrahydro-2-oxo-5-(phenylthio)-1H-1-benzazepin-1-yl]methyl]- (9CI) (CA INDEX NAME)



RN 158104-42-8 USPATFULL
CN [1,1'-Biphenyl]-2-carboxamide, 4'-[[2,3,4,5-tetrahydro-3-[[3-[(2-hydroxypropyl)amino]-3-methyl-1-oxobutyl]amino]-2-oxo-5-(phenylthio)-1H-1-benzazepin-1-yl]methyl]- (9CI) (CA INDEX NAME)



L52 ANSWER 26 OF 27 USPATFULL on STN
ACCESSION NUMBER: 94:40056 USPATFULL
TITLE: Benzo-fused lactams that promote the release of growth hormone
INVENTOR(S): Fisher, Michael H., Ringoes, NJ, United States
Schoen, William R., Edison, NJ, United States
Wyvratt, Matthew J., Mountainside, NJ, United States
DeVita, Robert J., Westfield, NJ, United States
PATENT ASSIGNEE(S): Merck & Co., Inc., Rahway, NJ, United States (U.S. corporation)

NUMBER KIND DATE

PATENT INFORMATION:	US 5310737	19940510
APPLICATION INFO.:	US 1993-12190	19930202 (8)
RELATED APPLN. INFO.:	Division of Ser. No. US 1992-839742, filed on 28 Feb 1992, now patented, Pat. No. US 5206235 which is a continuation-in-part of Ser. No. US 1991-673695, filed on 20 Mar 1991, now abandoned	
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	Granted	
PRIMARY EXAMINER:	Shah, Mukund J.	
ASSISTANT EXAMINER:	Sripada, Pavanaram R.	
LEGAL REPRESENTATIVE:	Rose, David L., DiPrima, Joseph F.	
NUMBER OF CLAIMS:	9	
EXEMPLARY CLAIM:	1	
LINE COUNT:	6705	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB There are disclosed certain novel compounds identified as benzo-fused lactams which promote the release of growth hormone in humans and animals. This property can be utilized to promote the growth of food animals to render the production of edible meat products more efficient, and in humans, to increase the stature of those afflicted with a lack of a normal secretion of natural growth hormone. Growth promoting compositions containing such benzo-fused lactams as the active ingredient thereof are also disclosed.

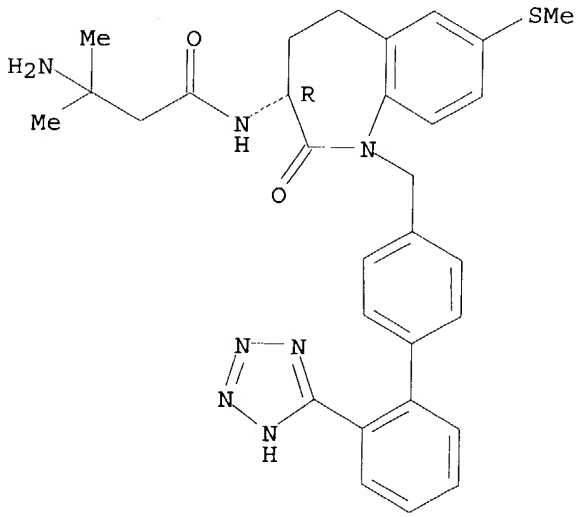
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

IT **145455-70-5P 145455-71-6P 145455-72-7P**
145455-73-8P 145552-97-2P 145552-98-3P
(preparation of, as growth hormone release promoter)

RN 145455-70-5 USPATFULL

CN Butanamide, 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-, (R)- (9CI) (CA INDEX NAME)

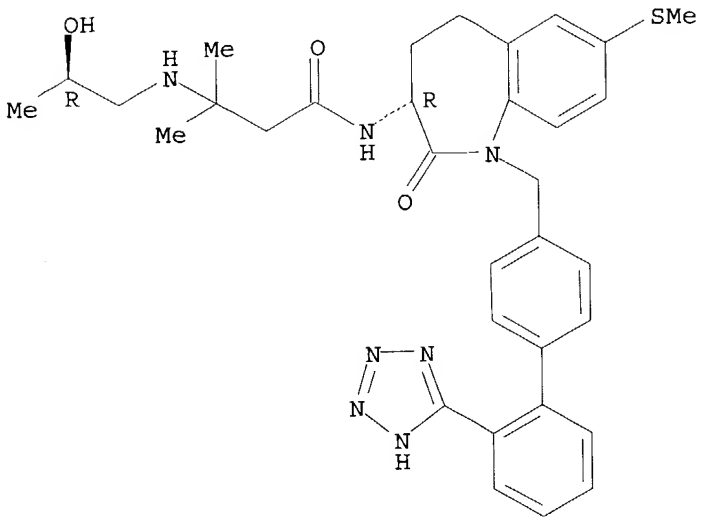
Absolute stereochemistry.



RN 145455-71-6 USPATFULL

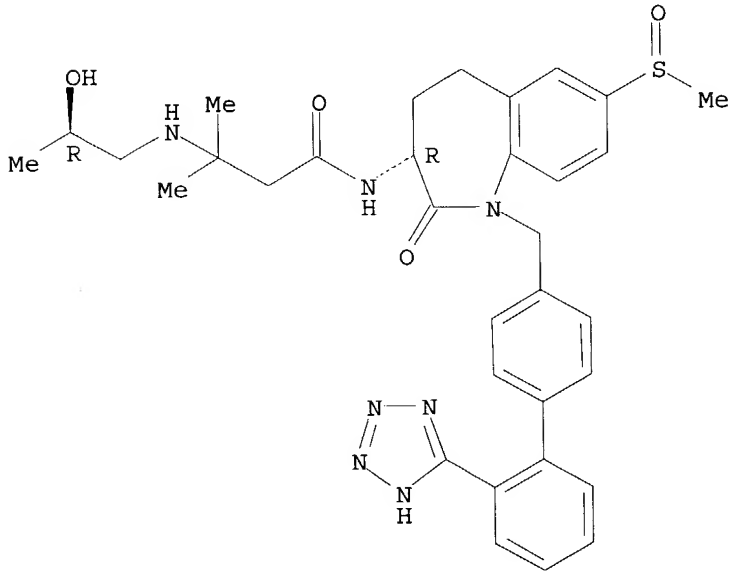
CN Butanamide, 3-[(2-hydroxypropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-, [R-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



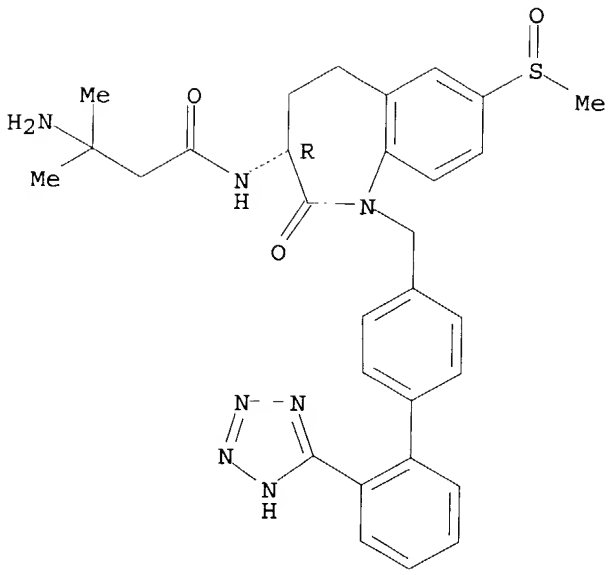
RN 145455-72-7 USPATFULL
CN Butanamide, 3-[(2-hydroxypropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-7-(methylsulfinyl)-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-, [3R-[3R*(R*)]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 145455-73-8 USPATFULL
CN Butanamide, 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-7-(methylsulfinyl)-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-, (3R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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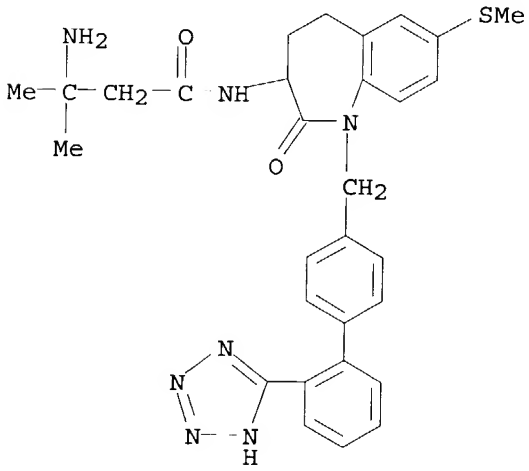
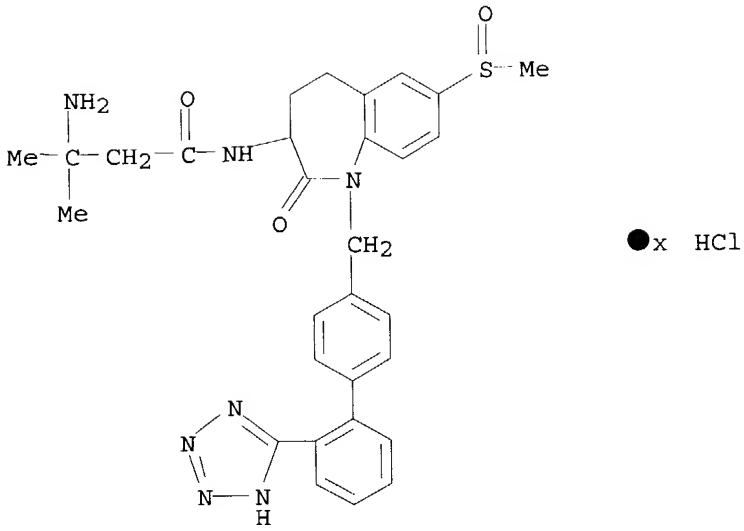
CN Butanamide, 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-, hydrochloride (9CI) (CA INDEX NAME)



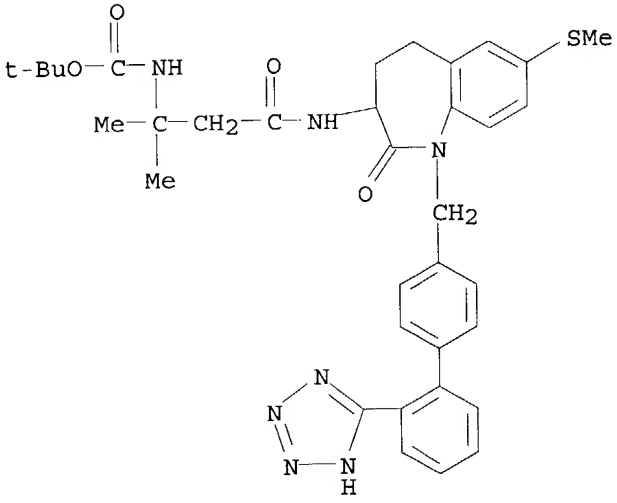
●x HCl

RN 145552-98-3 USPATFULL
CN Butanamide, 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-7-(methylsulfinyl)-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-, hydrochloride (9CI) (CA INDEX NAME)



IT **146429-18-7P 146429-19-8P**
(preparation of, as intermediate for growth hormone release promoter)
RN 146429-18-7 USPATFULL
CN Carbamic acid, [1,1-dimethyl-3-oxo-3-[[2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1-[[2'-[(triphenylmethyl)-1H(or 2H)-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]amino]propyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

PAGE 1-A



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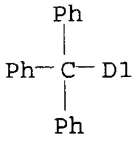
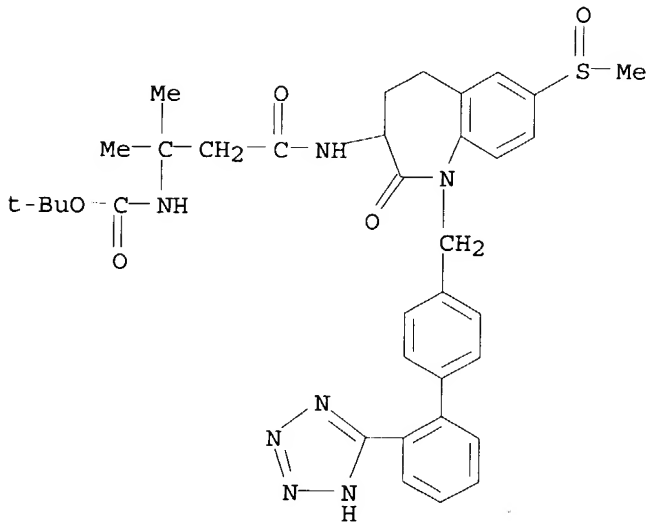


RN 146429-19-8 USPATFULL
CN Carbamic acid, [1,1-dimethyl-3-oxo-3-[[2,3,4,5-tetrahydro-7-(methylsulfinyl)-2-oxo-1-[[2'-[(triphenylmethyl)-1H(or 2H)-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]amino]propyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

PAGE 1-A



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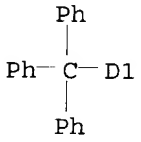


L52 ANSWER 27 OF 27 USPATFULL on STN

ACCESSION NUMBER:	93:33488 USPATFULL
TITLE:	Benzo-fused lactams that promote the release of growth hormone
INVENTOR(S):	Fisher, Michael H., Ringoes, NJ, United States Schoen, William R., Edison, NJ, United States Wyvratt, Matthew J., Mountainside, NJ, United States DeVita, Robert J., Westfield, NJ, United States
PATENT ASSIGNEE(S):	Merck & Co., Inc., Rahway, NJ, United States (U.S. corporation)

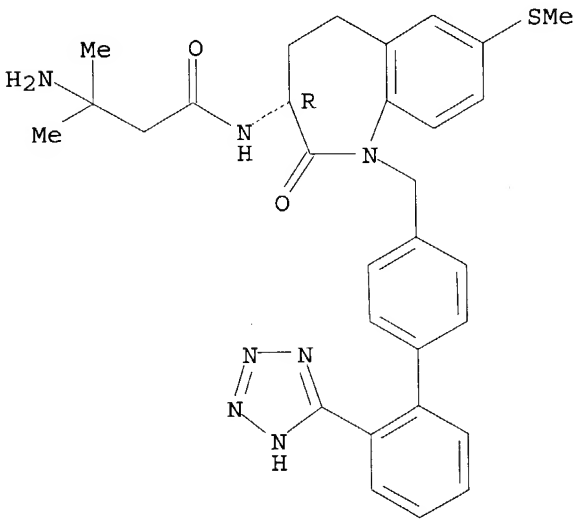
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5206235		19930427
APPLICATION INFO.:	US 1992-839742		19920228 (7)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 1991-673695, filed on 20 Mar 1991, now abandoned		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Berch, Mark L.		

LEGAL REPRESENTATIVE: Rose, David L., DiPrima, Joseph F.
NUMBER OF CLAIMS: 8
EXEMPLARY CLAIM: 1
LINE COUNT: 6831
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB There are disclosed certain novel compounds identified as benzo-fused lactams which promote the release of growth hormone in humans and animals. This property can be utilized to promote the growth of food animals to render the production of edible meat products more efficient, and in humans, to increase the stature of those afflicted with a lack of a normal secretion of natural growth hormone. Growth promoting compositions containing such benzo-fused lactams as the active ingredient thereof are also disclosed.

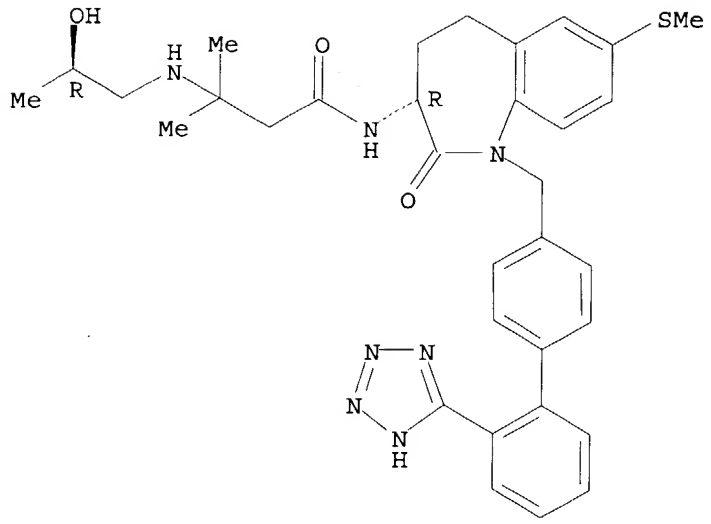
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **145455-70-5P 145455-71-6P 145455-72-7P**
145455-73-8P 145552-97-2P 145552-98-3P
(preparation of, as growth hormone release promoter)
RN 145455-70-5 USPATFULL
CN Butanamide, 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



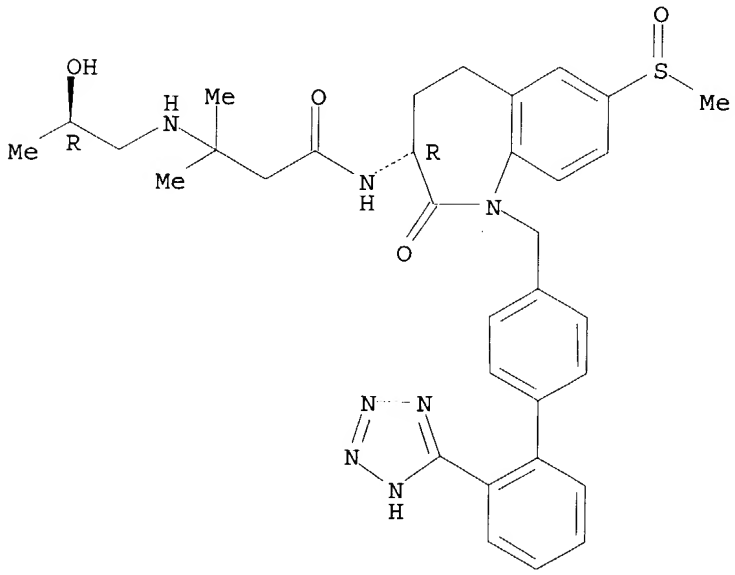
RN 145455-71-6 USPATFULL
CN Butanamide, 3-[(2-hydroxypropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-, [R-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



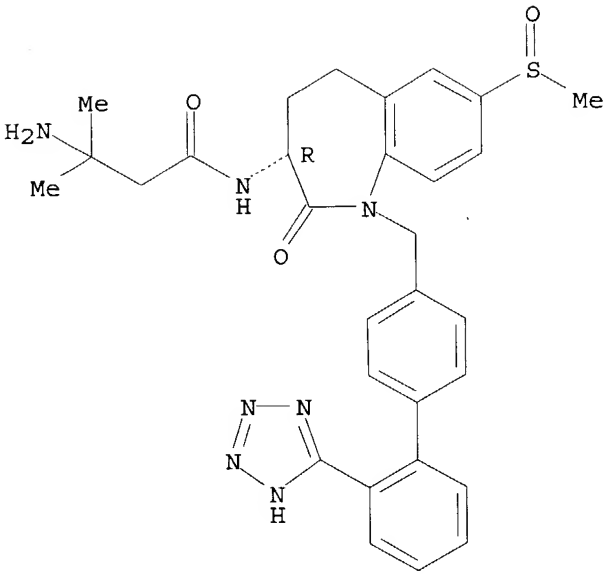
RN 145455-72-7 USPATFULL
CN Butanamide, 3-[(2-hydroxypropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-7-(methylsulfinyl)-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-, [3R-[3R*(R*)]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

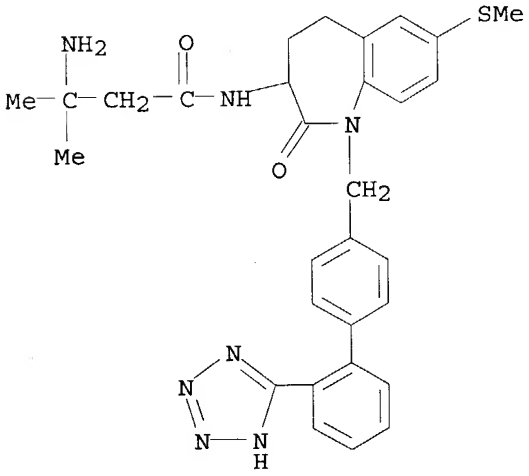


RN 145455-73-8 USPATFULL
CN Butanamide, 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-7-(methylsulfinyl)-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-, (3R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

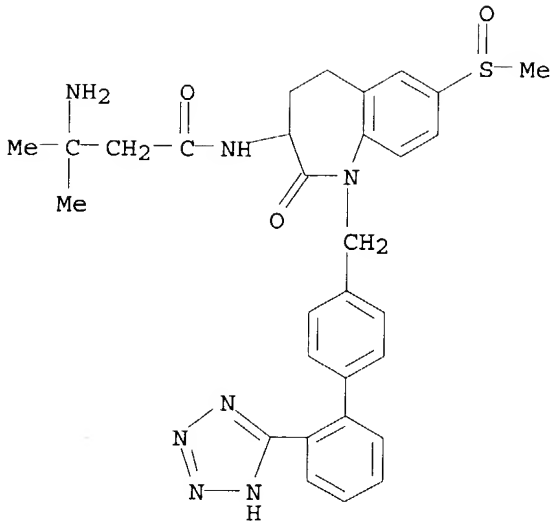


RN 145552-97-2 USPATFULL
CN Butanamide, 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-, hydrochloride (9CI) (CA INDEX NAME)



●x HCl

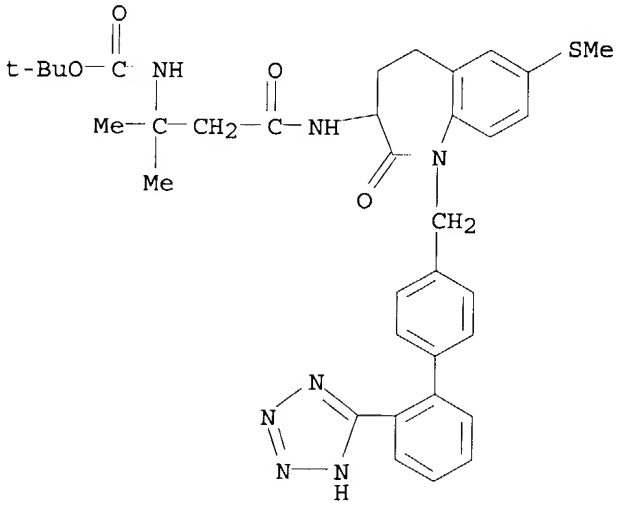
RN 145552-98-3 USPATFULL
CN Butanamide, 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-7-(methylsulfinyl)-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-, hydrochloride (9CI) (CA INDEX NAME)



● x HCl

IT **146429-18-7P 146429-19-8P**
(preparation of, as intermediate for growth hormone release promoter)
RN 146429-18-7 USPATFULL
CN Carbamic acid, [1,1-dimethyl-3-oxo-3-[[2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1-[[2'-[(triphenylmethyl)-1H(or 2H)-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]amino]propyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

PAGE 1-A



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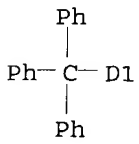
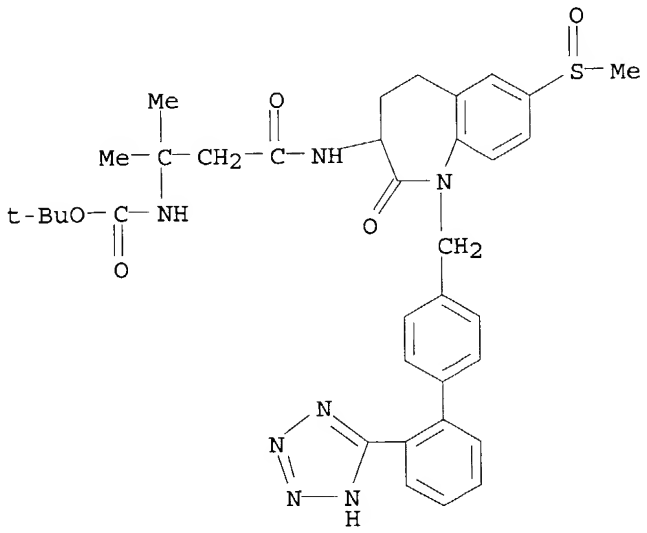


RN 146429-19-8 USPATFULL
CN Carbamic acid, [1,1-dimethyl-3-oxo-3-[[2,3,4,5-tetrahydro-7-(methylsulfinyl)-2-oxo-1-[[2'-[(triphenylmethyl)-1H(or 2H)-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]amino]propyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

PAGE 1-A



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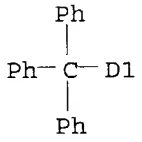

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FILE 'STNGUIDE' ENTERED AT 11:46:12 ON 27 NOV 2004
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FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Nov 19, 2004 (20041119/UP).

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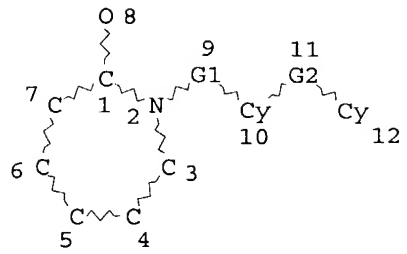
L2 STR



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DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 14

STEREO ATTRIBUTES: NONE
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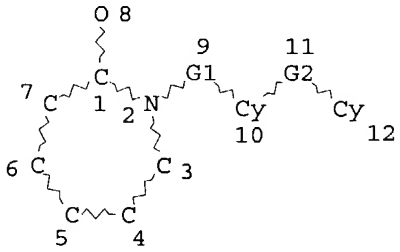

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CONNECT IS E1 RC AT 8
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 14

STEREO ATTRIBUTES: NONE
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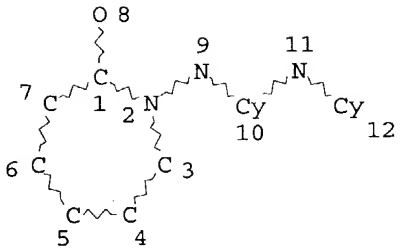

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CONNECT IS E1 RC AT 8
DEFAULT MLEVEL IS ATOM
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NUMBER OF NODES IS 12

STEREO ATTRIBUTES: NONE

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L29	58	SEA	FILE=HCAPLUS	ABB=ON	PLU=ON	L22
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